HEALTH EFFECTS OF
PROJECT SHAD
CHEMICAL AGENT:

**URANINE DYE**

[SODIUM FLUORESCEIN]
[CAS # 518-47-8]

[Soluble salt of FLUORESCEIN]
[CAS # 2321-07-5]

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Contract No. IOM-2794-04-001
Health Effects of Uranine Dye [Sodium Fluorescein]
SPECIAL NOTE ON PSYCHOGENIC SEQUELAE OF PERCEIVED
EXPOSURE TO BIOCHEMICAL WARFARE AGENTS

This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates, by reference and attachment, a supplement entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress experienced personally from actual or perceived exposure to chemical and biological weaponry. Because awareness of exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic health consequences of perceived exposure may be regarded as additional health effects arising from the exposure to Project SHAD agents. This reasoning may also apply to simulants and tracers. Therefore, a general supplement has been created and submitted under this contract to address possible psychogenic effects of perceived exposure to biological and chemical weaponry.

Because such health effects are part of a recent and growing public concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.
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I. EXECUTIVE SUMMARY

When Johann Strauss composed the classic waltz, the “Beautiful Blue Danube” in 1867, he could not have known that, only ten years later, a famous part of the blue Danube – its “sinks” in the upper river region -- would turn green. The color change would be temporary and artificial, however, as it was the result of one of the first uses of fluorescein, a fluorescent tracer dye. Soon thereafter its more water-soluble sodium salt would circulate under the industrial name Uranin or Uranine. The dye would go on to have enormous and still-continuing important medical and environmental uses.

Uranine Dye is known in more scientific circles as sodium fluorescein (or fluorescein sodium), as well as disodium fluorescein. It has the chemical formula C_{20}H_{12}O_{5}-2Na and the Chemical Abstracts Service (CAS) Registry Number 518-47-8. The name fluorescein is often used carelessly and interchangeably with the various compounds derived from fluorescein, including sodium fluorescein/uranine. In this report, therefore, the term uranine is used to mean specifically the sodium salt of fluorescein (CAS #518-47-8). The term fluorescein is used to mean the acid compound, fluorescein, which is identified by the CAS #2321-07-5 and has the formula C_{20}H_{12}O_{5}.

Uranine is freely soluble in water and alcohol; after dissolution it emits a bright yellowish-green fluorescence, especially under blue light. This indicator dye tends to appear more green the more alkaline the medium. Its use in ocular therapy is long-established: first synthesized in 1871, by 1882 uranine was being used as an injected dye for examining ocular fluid dynamics in cases of glaucoma. In 1959, it saw its first use in its most widespread application, intravenous fluorescein angiography, considered a vital advance in the examination of the pathophysiology of retinal diseases. Uranine is also used in topical ocular diagnostic and therapeutic applications.

Uranine is useful as a dye to trace cerebrospinal fluid leaks during surgery. Outside of medical uses, uranine is also used to trace the flow of subterranean waters. It functions also as a dye in cosmetics. In Project SHAD, uranine dye was used as a tracer for the biological agent Staphylococcal Enterotoxin Type B. Increasingly, it is used as a tracer for the activity of inhaled particulates.

Typically, injected uranine takes less than 20 seconds to circulate in the blood stream. When absorbed, uranine is rapidly metabolized thorough glucuronidation in the liver. 80% of the dose is usually metabolized within in one hour. The pharmacodynamics and toxicodynamics of fluorescein are not well understood.

Animal studies show very low toxicity. At very high doses, death occurs from CNS depression, and one study suggests sensitivity to light exposure.

There exists a great deal of clinical data on the effects of injected uranine. Systemically, the common responses to injection range from a non-toxic yellowing of the skin to acute severe reactions up to and including (in very rare circumstances) mortality. The adverse effects of fluorescein angiography are usually grouped into three broad categories: mild,
moderate, and severe. Males appear to be more susceptible to adverse effects than females.

The main mild adverse effects are transient nausea, vomiting, local pruritus, extravasation and some allergic reactions. Urticaria, lowered pulse rate, syncope, dyspnea, and local effects at the injection site and region (thrombophlebitis, subcutaneous granuloma, neuritis) are among the more moderate reactions. The more severe reactions include respiratory effects like laryngeal edema, pulmonary edema, bronchospasms, anaphylaxis along with certain cardiac effects like basilar artery ischemia, circulatory shock, myocardial infarction and cardiac arrest. Tonic-clonic seizure is a noted neurologic reaction. Death can occur, though very rarely, about one case being reported per year. The main risk factor in such reactions appears to be a prior adverse reaction to uranine treatment.

The main noted risk factor in a fluorescein angiography appears to be a prior adverse event.

Local administration affects certain systems in observed ways. Topical ocular administration has produced transient discoloration and conjunctival chemosis. This occurred only when accompanied by active inflammatory disease. When uranine has been employed intrathecally as a tracer for cerebrospinal fluid leaks in surgery, suboccipital punctures have resulted in cases of grand mal seizure, which did not seem to occur when suboccipital punctures were stopped. Lumbar administration has yielded severe neurotoxic signs: temperature elevation, headache, nausea, vomiting, dizziness, nuchal pain, grand mal seizures.

Increasing interest in inhalation drug therapy has resulted in use of uranine in pulmonary exposure experiments. The kinetics of such exposure include very rapid absorption by the lung and without any significant metabolism inside the lung. No studies or reports of toxic effects from this type of exposure have been found. A recent correspondence from a leading investigator in the field reports that although there is an absence of existing studies on the toxicity of inhalation exposure to uranine, studies with aerosolized uranine have been ongoing for several years in European hospitals with no untoward clinical effects of any kind known.

The only known studies of carcinogenicity go back to two tests in Japan in the 1950s. Cancerous tumors at the application site were elicited after chronic application of large concentrations of uranine. These results have been deemed equivocal evidence only of tumorigenicity by the Registry of Toxic Effects of Chemical Substances (RTECS). A screen of for the carcinogenic/mutagenic potential of compounds using DNA cell binding assay gave inconclusive results for uranine. Other results from a genetic toxicity screen to predict carcinogenicity, Salmonella microsome mutagenesis, chromosome aberration, sister-chromatid exchange and mouse lymphoma mutagenesis assay were compared for consistency to assess DNA damage from chemicals. Uranine yielded either negative or equivocal results for tumorigenicity and genetic toxicity and positive activity both with and without exogenous metabolic activation for sister chromatid exchange.
Neither uranine nor fluorescein has been found by the International Agency for Research on Cancer (IARC), or any other authoritative agency, to be carcinogenic. No human cancer effects reports or studies have been found.

Psychogenic reactions brought on by the manner of uranine administration have been suggested to explain some adverse effects. A variation in response to fluorescein angiographies by gender has been noted in that regard. Observed reactions like syncope, hypotension, and lowered pulse rate (vasovagal effects) have been suggested to be arise from the nature of the treatment which is the internal injection of a discoloring and glowing substance while cameras are brought to peer into the inner eye along with strange bodily effects (e.g. skin discoloration) that can occur. Other psychogenic issues, such as the general stressor reactions to perceived exposure to a contaminant in biological and chemical warfare testing, are treated in the supplement under this contract “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents”.

Standard prophylaxis is to have an emergency tray and oxygen supply handy when a uranine procedure is performed. It has been shown that persons with allergic sensitivities benefit from a prophylactic administration of antihistamines. Epinephrine followed by diphenhydramine hydrochloride may be necessary for patients who have a hypotensive reaction.

Secondary sources (outside the field of ophthalmology) do not contain a great deal of data on uranine except in the context of fluorescein angiography. The confusing and careless interchangeable use among fluorescein, sodium fluorescein, the term uranine (dye) can render research problematic. The Hazardous Substances Data Bank conflates acid fluorescein with the disodium salt fluorescein (i.e. uranine) in the same entry. Patty’s Toxicology contains only a brief reference to fluorescein angiography and no section on fluorescein or sodium fluorescein (uranine).
II. BACKGROUND DATA

Identification & Physical Chemistry

Project SHAD Chemical Agent Name: Uranine Dye

CAS#: 518-47-8

Chemical Formula: $C_{20}H_{12}O_{5}$-2$\text{Na}$ (Uranine -- Fluorescein Sodium/Sodium Fluorescein); $C_{20}H_{12}O_{5}$ (Fluorescein).

Chemical Structure:

![Chemical Structure Diagram]

More Commonly Appearing Name(s): Sodium Fluorescein, Fluorescein Sodium, Disodium Fluorescein

Alternate Names: 3',6'-Dihydroxyxyspiro(isobenzofuran-1(3H),9'-(9H)xanthen)-3-one, CI 45350:1, D & C Yellow no. 7, Fluorescein, Fluorescein [BAN:JAN], 11712 Yellow, 3',6'-Dihydroxyfluoran, 3',6'-Dihydroxyxyspiro(isobenzofuran-1(3H),9'(9H)-xanthen)-3-one, 3,6-Dihydroxyxyspiro(xanthene-9,3'-phthalide), 3,6-Fluorandiol, BRN 0094324, Benzoic acid, 2-(6-hydroxy-3-oxo-3H-xanthen-9-yl)-, Benzoic acid, o-(6-hydroxy-3-oxo-3H-xanthen-9-yl)-, C.I. 45350:1, C.I. Solvent Yellow 94, CCRIS 7076, CI 45350:1, D and C Yellow No. 7, D+C Yellow No. 7, EINECS 219-031-8, Fluoran, 3',6'-dihydroxy-, Fluorescein Red, Fluorescein acid, Fluoresceine, HSDB 2128, Hidacid fluorescein, Japan Yellow 201, Resorcinolphthalein, Soap Yellow F, Sodium Fluorescite, Solvent Yellow 94, Spiro(isobenzofuran-1(3H),9'-{(9H)xanthen)-3-one, 3',6'-, dihydroxy-, Uranine Yellow, Yellow fluorescein, Zlut kysela 73 [Czech], Fluorescein, disodium salt

Molecular Weight: 376.28

Melting Point: 315 – 395°C

(Sources: ChemID-TOXNET 2004; RTECS 2004)
Uranine dye, more commonly known as sodium fluorescein (or fluorescein sodium), is the salt of the fluorescent indicator dye fluorescein, and bears the chemical formula C_{20}\text{H}_{12}\text{O}_{5}\cdot 2\text{Na}. Unlike the acid fluorescein (CAS # 2321-07-5), uranine is freely soluble in water and alcohol. The yellowish-red uranine, when in solution, fluoresces bright yellowish-green when excited by blue (480nm) wavelengths. This indicator dye is influenced by pH, emitting in the green wavelengths as the medium becomes more alkaline (Hogan and Zimmerman, 1977; Borah et al, 2003).

In order to prevent confusion between the two compounds fluorescein and sodium fluorescein, in this report the name uranine will be used for the compound sodium fluorescein (CAS # 518-47-8), and the acid fluorescein (CAS # 2321-07-5) will be referred to simply as "fluorescein". It should be noted, however, that the name uranine is used primarily in Europe rather than the name sodium fluorescein. American and British writing tend refer to sodium fluorescein only as "fluorescein", which can lead to imprecision (Field et al 1995).

Use

Fluorescent dyes are frequently used as water tracers. Fluorescein was first synthesized in 1871; by 1877, it was being used to trace the sinking portions of the upper Danube river. A more water-soluble salt form of the dye was soon produced under the trade name Uranine. It is still considered one of the best fluorescent dyes for the tracing of water flow (Crawford Hydrology Laboratory 2004).

Uranine's use in ocular diagnostic therapy is also long-established. By 1882 it was being used as an injected dye for examining ocular fluid dynamics in cases of glaucoma. In 1959, uranine saw its first use in the procedure fluorescein angiography. This most-widespread of uranine's applications is considered a vital advance in the examination of the pathophysiology of retinal diseases. As many as 10 million fluorescein angiographies are performed each year in the U.S. alone (Waller 2003).

The procedure for fluorescein angiography is to take a baseline photograph then compare that with the fluorescence patterns that follow the injection (usually in the antecubital vein) and arrival of the dye. Exciter filters illuminate the interior of the eye with 465-490 nm wavelength. Hyperfluorescence indicates leaks, pooling, staining, abnormal vessels and transmission defects. Hypofluorescence indicates barriers and filling defects (capillary closures, retinal vascular occlusions) (Sowka 2004).

Uranine is also used topically in the fitting of hard contact lenses and in other ocular diagnostic and therapeutic areas, particularly in corneal challenges (Hogan and Zimmerman 1997).

In other medical applications, uranine dye has been used to trace cerebrospinal fluid leaks during surgery, to trace pulmonary deposition of aerosols for designing inhaled drugs, and in thoracoscopy (Lue and Manolidis 2004; Hogan and Zimmerman 1997; Pillai et al
Finally, in addition to medical and environmental uses, the dye is also used in cosmetic formulations. (Merck Index 1995).

In Project SHAD, uranine dye was used as a tracer for the biological agent Staphylocooccal Enterotoxin Type B. A two percent concentration of uranine was incorporated into the staphylococcal enterotoxin, during the drying cycle at the production plant. The dye served as a tracer for the agent (Project 112 2004).

**Kinetics**

Injections of uranine for fluorescein angiography is usually 5ml of a 10% solution or 2ml of a 25% solution. Typically, injected uranine takes less than 20 seconds to reach its destination (Sowka 2004).

Injected uranine binds to plasma proteins and erythrocytes in the blood. It then is rapidly metabolized by glucuronidation in the liver. Within an hour, 80% of the dose is metabolized. The resultant metabolite, fluorescein glucuronidate, and the uranine are then eliminated by the kidneys (Hogan and Zimmerman 1997).

Orally-administered uranine has a longer absorption time and is eliminated in urine within 48 hours, however, the pharmacodynamics and toxicodynamics of uranine are not well-understood. (Hogan and Zimmerman 1997).

Because uranine is so water-soluble, it cannot pass through, or be topically absorbed by, lipid membranes, but it can pass between cells into extravascular spaces. (Hogan and Zimmerman 1997).
III. HEALTH EFFECTS/TOXICITY

Overview

A great deal of data exists on the human effects of injected uranine. Animal studies suggest that reproductive or teratogenic effects do not occur; there are no equivalent human studies. No studies have been found of human carcinogenicity.

It is also suggested that there may be an allergenic effect from uranine exposure, but this is not supported by tests taken during reactive episodes. There are no known adverse cross-reactions to other drugs (Hogan & Zimmerman 1997). Determining toxicity is complicated by several factors. Other substances used in administration might affect results. The role of allergy and prior sensitization is unclear. The effects of local injection pressure may cause pain or other reactions (Hogan & Zimmerman 1997). The key risk factor for toxic reaction is a prior adverse event (Hogan & Zimmerman 1997).

Genders appear to react differently to uranine: a higher number of males experienced adverse effects than females (Green et al 1976). Ethnic origins influence reactions: black, Asian, Sino-Asian and mixed races have greater adverse reactions (McLauchlan et al 2001) Another confounding factor is the possibility of psychogenic effects.

Acute Animal Toxicity

Toxicity profiles for acute administration of uranine are as follows. Death from uranine was usually due to CNS depression, which included decreased motor control and decreased respiration.

LD$_{50}$ is lethal dose, 50% kill.

**Oral administration:**
LD$_{50}$ rats = 6721 +/- 1.26 mg/kg  
LD$_{50}$ mice= 4738 +/-1.23 mg/kg (Yankell and Loux 1977)

Pregnant rabbits: no maternal/fetal toxicity up to 250mg/kg  
Pregnant rats: no maternal/fetal toxicity up to 1500 mg/kg  
(Burnett and Goldenthal 1986)

**Intravenous (i.v.) administration:**
5ml/kg of 10% uranine in pregnant rats: detected in fetus in 15min; none detected at 24h (Salem et al 1979)
Rat: 400mg/kg uranine every 72 hrs after 28d increased hemoglobin and hematocrit
Dogs: at the highest dose (400mg/kg), no change in organ weights, hematocrit, urinalysis, and ocular structures increase in salivation and emesis (McDonald et al 1974)
Adverse Effects of Intravenous Uranine

Reactions to uranine occur within a few hours of exposure (Borah et al, 2003). Areas of adverse effects can range from localized through regional to systemic. Systemically, the common responses to injection range from a non-toxic yellowing of the skin to acute severe reactions, up to and including in very rare cases, mortality (Flewellen 1980).

A survey of 221,781 cases in 1984 categorized the adverse effects of fluorescein angiography by intravenous administration into three broad categories: mild, moderate, and severe. Mild had the highest frequency rate and severe the lowest (Yannuzzi et al 1986):

Mild adverse effects include transient nausea, vomiting, local pruritus, extravasation, yellow skin discoloration, and some allergic reactions have been observed in humans.

Moderate reactions are urticaria, lowered pulse rate, syncope, dyspnea, and local effects at the injection site and region (thrombophlebitis, subcutaneous granuloma, neuritis).

Severe reactions were encountered as respiratory disorders like laryngeal edema, pulmonary edema, bronchospasm, anaphylaxis and as cardiac effects like basilar artery ischemia, circulatory shock, atrial fibrillation, acute myocardial infarction and cardiac arrest. (Borah et al 2003; Kirson and Wilson 1987; Deglin et al 1977) Tonic-clonic seizure is a noted severe neurologic reaction (Yannuzzi, et al. 1986).

An earlier survey suggested a higher rate and intensity of adverse effects. Serious or fatal toxic episodes in the course of fluorescein angiography were assessed through a survey involving responses from 260 clinics in 30 different countries. The survey reported on 594,687 angiographies. The incidence of fatal events was one case per 49,557 angiographies, and of serious events there was one case per 18,020 angiographies. The total number of incidents was 45 or one case per 13,215 angiographies (Zographos 1983).

Topical Application

Reactions to topically applied uranine can include transient discoloration of the skin or conjunctiva (Flewellen 1980). There is one recent report on a systemic adverse reaction to topically applied uranine (Anderson 2002), but the conclusions were criticized in a subsequent commentary (Waller 2003).

In direct administration to the eye, unilateral conjunctival chemosis and injection began or increased, and conjunctival yellowish discoloration was seen in cases where an active inflammatory disease was present (Foster et al 2004).
**Cerebrospinal Fluid Injection**

When intrathecal uranine was employed in surgical procedures as a tracer for cerebrospinal fluid leaks, suboccipital punctures resulted in 3 cases of grand mal seizure which did not seem to occur again after suboccipital punctures were stopped (Moseley 1978). Lumbar administration of intrathecal contrast media has yielded severe neurotoxic signs: temperature elevation, headache, nausea, vomiting, dizziness, nuchal pain, grand mal seizures and apnea (Mees 1982; Keerl et al 2004; Coeytaux et al 1999; Moseley 1978).

**Phototoxicity**

Cutaneous erythema, edema, and pain in areas of solar exposure followed exposure to uranine after 1 hour. One case manifested a mild epidermal desquamation with prolonged discomfort (Danis et al 1997).

Animals exposed to uranine and intense light exhibited marked visual and dermal cell damage (Myata et al 1972).

**Inhalation Toxicity**

There is considerably less in the literature on pulmonary effects of uranine. Most concern animal models (rat, dog, guinea pig) of pulmonary absorption tested to examine the inhalant delivery of drugs. Uranine is rapidly absorbed in the lungs and in the respiratory tract, and is affected by the presence of surfactants (Clark and Byron 1985; Byron and Clark 1985; Niven and Byron 1990). It is not metabolized in the lung, Inhaled uranine is excreted in the urine (Pillai et al 1998).
In a very recent study, uranine was used as a tracer in thoracoscopy to determine air leakage (Noppen et al, 2004). Following is the author's reply to an inquiry authorized by the Principal Investigator of this review on uranine's inhalation toxicity (note: the use of the term "fluorescein" here actually refers to "sodium fluorescein"/uranine.)

From: Marc Noppen <marc.noppen@az.vub.ac.be>
To: cri@ix.netcom.com
Subject: Re: Aerosolized fluorescein toxicity/adverse effects
Date: Sep 23, 2004 3:07 AM

I am not aware of any publications on the safety/toxicity of inhaled fluorescein. I do now [sic] that this has been done for years in several European hospitals (e.g., St marguerite in Marseille, prof. Boutin [sic]) without any reports of toxicity.

Kind regards
Marc Noppen

Reproductive Toxicity

A teratogenicity study on pregnant rabbits given doses equivalent to those normally used in humans did not result in abortions or birth defects (McEnerney et al 1977). A similar study with pregnant rats also showed no teratogenic effects (Salem et al 1979).

Renal Toxicity

No clear data exists on toxicity to the renal system. There is one study where excised canine kidneys were perfused with uranine, temporarily cryopreserved, then retransplanted back into the dogs. Renal function was unharmed by uranine perfusion. (Burleson et al 1981) Generally, caution is recommended using uranine on patients with renal failure (Borah et al 2003; Hogan and Zimmerman 1997).

Carcinogenicity/Genotoxicity

There are very few studies on uranine's carcinogenicity.

Two pre-1960 Japanese reports described inducing a sarcoma in rats by uranine, producing subcutaneous tumors at the site of repeated injections of very high doses (Umeda 1954; Umeda 1956). These tests have proven sufficient for the Registry of Toxic Effects of Chemical Substances (RTECS) to deem uranine an equivocal tumorigen.

A screen for the carcinogenic/mutagenic potential of compounds using DNA cell binding assay gave inconclusive results for uranine (Kubinski et al 1981)
Results from a genetic toxicity screen to predict carcinogenicity using tests for *Salmonella*/microsome mutagenesis, chromosome aberration, sister chromatid exchange and mouse lymphoma mutagenesis were compared for consistency to assess DNA damage from chemicals. Uranine yielded either negative or equivocal results for tumorigenicity and genetic toxicity, and yielded positive activity both with and without exogenous metabolic activation for sister chromatid exchange (Tennant et al.1987).

There is no record of any report, determination, or investigation by any authoritative agency, including the International Agency for the Research of Cancer (IARC) (see http://www.iarc.fr), on the carcinogenicity of uranine or of fluorescein. No human clinical or epidemiological studies have been found reporting cancer as an effect of uranine exposure.
IV. PSYCHOGENIC EFFECTS

The variation in gender response to uranine administration is noted in regard to the question of possible psychogenic effects. Reactions like syncope, hypotension, and lowered pulse rate (vasovagal effects) might be psychogenic, consequences of the unusual nature of fluorescein angiography treatment and its strange bodily effects (Chazan et al 1971; Greene et al 1976). Other psychogenic issues, such as the general stressor-induced reactions that may occur after perceived exposure to a contaminant associated with biological and chemical warfare testing, are treated in the supplement “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents”.

V. TREATMENT & PREVENTION

Standard prophylaxis is to have an emergency tray and oxygen supply handy when a fluorescein procedure is performed. It has been shown that persons with allergic sensitivities may benefit from a prophylactic administration of antihistamines (Ellis et al 1980). Epinephrine followed by diphenhydramine hydrochloride may be necessary for patients who have a hypotensive reaction. (Hogan and Zimmerman 1997)

It is recommended to also have available emergency medicines (antihistaminics, steroids, aminophylline, etc.) and a physician's presence during fluorescein angiography (Borah et al 2003).
VI. SECONDARY SOURCE COMMENT

Secondary sources (outside the field of ophthalmology) do not contain a great deal of data on fluorescein (and use of the term uranine or urane dye is rare and inconsistent). Patty’s Toxicology contains only a brief reference to fluorescein angiography and contains no discussion of uranine or fluorescein (Bingham et al 2001).

The issue of terminological imprecision in the identity of uranine is illustrated by the following entry from a standard information source. The Hazardous Substances Data Bank (HSDB) of TOXNET at the National Library of Medicine contains a complete confusion of the compounds fluorescein and fluorescein sodium (uranine), citing both under the same entry as synonyms and omitting entirely the CAS number of the latter (emphasis added, below):

**FLUORESCEIN**
CASRN: **2321-07-5**
For other data, click on the Table of Contents
Best Sections
Formulations/Preparations:
/FLUOR-I-STRIP (AYERST, FUL-GLO & **FLUORESCEIN SODIUM** (BARNES-HIND), FLUORESEPTIC (SOFTCON PRODUCTS), FLUORESCINE SODIUM & FLUORESCITE (ALCON), **FLUORESCEIN SODIUM** & FUNDUSCEIN (SMP); AVAILABLE MIXT: FLURESS (BARNES-HIND)/
/FLUORESCEIN SODIUM/

VII. BIBLIOGRAPHY WITH ABSTRACTS

{This bibliography may contain supplemental material of note, beyond those works cited in the text. Abstracts are printed verbatim or otherwise how they are provided by the original source, catalogue or database. Errors in form and content of the abstracts are strictly those of the providing source.}


1. Fluorescein angiography is a relatively noninvasive diagnostic test which provides the ophthalmic practitioner with anatomic and physiologic information about the ocular structures. 2. Once the dye solution is injected, the photographer observes the fundus through the camera until it appears in the retinal vessels. Photographs are then taken in a rapid sequence. 3. The retinal arteries fill rapidly and evenly within two seconds following the initial choroidal flush. The dye circulates through the whole arterial tree in the body, and in the late stage angiogram recirculation can be seen in the retinal blood vessels.


Since its introduction, fluorescein angiography has been widely used to investigate diseases of the ocular fundus. A case of fatal acute myocardial infarction after intravenous fluorescein angiography is presented. This appears to be the first case documented by autopsy in which the findings are compatible with myocardial infarction as the cause of death. Although there are no known contraindications for fluorescein angiography in patients with a history of cardiovascular disease, the indications for this elective procedure should be carefully reviewed in such patients. Adequate emergency resuscitation equipment should be available in the fluorescein angiography suite.

A case report, differential diagnosis, and discussion of idiopathic central serous choroidopathy (ICSC) are presented. Procedures, advantages and disadvantages of oral and intravenous fluorescein angiography are discussed. Oral fluorography may be used to reliably diagnose ICSC and other late-staining disease processes.


The clinician must be the ultimate medical detective when dealing with chronic optic neuropathies. History taking is crucial. Clinical examination may require supplementation with visual field testing, fluorescein angiography, ocular and orbital ultrasound imaging, CT and MR imaging, blood test data, and cerebrospinal fluid or tissue biopsy data to determine the specific diagnosis. This supplementation is labor-intensive and time-consuming; the visual loss usually will progress throughout the process, frustrating and frightening the patient and physician. The final common pathway is gradual optic atrophy; the appearance of the optic nerve is rarely adequate to determine the cause of the visual loss. This article includes tables that review diagnostic aids and therapies, and lists the frequency with which several disease entities were encountered over 15 years in one tertiary care neuro-ophthalmic practice. If a specific cause is discernible, then a specific therapy may be available. This approach has the best chance of saving the patient's vision with the least toxicity caused by erroneous trials. By necessity, the work-up for these patients is expensive, but the cost of not pursuing the cause is irrevocable, permanent blindness.


The results of laboratory tests performed after fluorescein angiography may be erroneous

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because of interference by intravenous fluorescein. We investigated this potential interference in four adults at intervals of five minutes, three hours, six hours, and 12 hours after fluorescein injection. We used a panel of serum and urine chemistry tests on seven commonly used instruments. A significant change in the reported concentration of a serum or urine analyte was defined as a result beyond +/- 3 coefficients of variation of the preinjection baseline value for the test on a specific instrument. The determinations of creatinine, total protein, cortisol, digoxin, quinidine, and thyroxine in serum were affected by intravenous fluorescein. The urine tests were unaltered. The physician must be aware of the problem of interpreting clinical chemistry results after fluorescein angiography.

Borah et al 2003 Complications of fluorescein angiography – retrospective analysis of 11,800 cases. AIOC Proceedings 386-388

During fluorescein angiography, sodium fluorescein dye intended for intravenous use was inadvertently injected into an artery in the antecubital fossa. An immediate and dramatic orange discoloration of the skin distal to the injection combined with intense burning pain of the right forearm and hand were noted. The patient was treated with ice packs and analgesics. The fluorescein angiogram showed a delayed arm to eye circulation time, but was of normal quality. There were no long-term complications.


Fluorescein angiography carries with it a variable incidence of nausea and vomiting. We investigated a method of prophylaxis against this side effect. One hundred patients undergoing fluorescein angiography were pretreated in a double-masked, randomized fashion with either 20 mg of intravenous metoclopramide hydrochloride or an equal volume of normal saline solution. The metoclopramide-treated group demonstrated a statistically significant decrease in the incidence of nausea and vomiting. Eleven (22%) of the control group and three (6%) of the metoclopramide-treated group had this complication. Metoclopramide is an effective drug when used prophylactically in selected patients undergoing fluorescein angiography.

Our experience with intravenous fluorescein involved 38 administrations in 29 patients. In all, 24 percent were associated with a drop in blood pressure of 20 mmHg or more and 8 percent with a blood pressure fall of 60 mmHg or more. We believe that physicians using fluorescein in bolus form should be aware of the problem of blood pressure reduction and be prepared to take restorative measures when necessary.


Methylene blue, indigo carmine, and fluorescein dyes were evaluated to determine their effect on the dog kidney. Methylene blue and indigo carmine were administered intravenously and intraarterially to the in situ vascularized kidney and serial histologic appearance of the kidney was determined. The three dyes were administered intraarterially to excised kidneys that were then preserved for 1 hour in the cold and autotransplanted; and finally the three dyes were administered to the perfusate of excised kidneys that were perfused for 18 hours by cryoperfusion with an albumin perfusate and then autotransplanted. Renal function and histology were determined 5 days after autotransplantation. Methylene blue dye did not damage the in situ vascularized kidney as judged by renal histology. However, administration of methylene blue to the ex vivo kidney that was subsequently short term cold stored or perfusion stored was associated with marked apparent ischemic damage of the organ. Indigo carmine dye did not adversely affect either the in situ vascularized kidney or the short term cold stored kidney. However, with perfusion storage, indigo carmine produced apparent vasoconstriction that led to perfusion failure. Fluorescein dye was not harmful to the kidney either during short term cold storage or during perfusion preservation. It is concluded that fluorescein is the dye of choice for evaluating the vascular anatomy or macroperfusion status of the kidney.


Adverse reactions were noted in 241 (4.82%) of 5,000 consecutive intravenous fluorescein angiographies of the retina. The most frequent adverse reactions were nausea (2.24%), vomiting (1.78%), and urticaria/pruritus (0.34%). No life-threatening reactions were noted. No significant difference in the rate of adverse reactions was found when angiography using 10% fluorescein was compared with angiography using 25% fluorescein.

The isolated, perfused rat lung preparation was modified to allow characterized solid aerosol delivery. Deposition and airway-to-perfusate transfer of disodium fluorescein from 3-4 micron dace solid aerosols were studied under different ventilatory regimes. The lungs inhaled from an aerosol stream of constant concentration via a tracheal cannula. Air displacement from a sealed artificial thorax housing the lungs provided the driving force for inhalation. The lungs were suspended in a physiologically normal position and both left and right sides of the heart were cannulated for constant rate perfusate flow. Fractional deposition was inversely proportional to respiratory frequency implying that sedimentation was the primary deposition mechanism. Increasing tidal volumes similarly enhanced the ratio of amount deposited/amount administered. Fluorescein transfer to the perfusate occurred from the lung regions containing intact vasculature, was apparent first-order, and independent of perfusate flow. The average rate constant for transfer was 0.057 +/- 0.02 min-1 (t1/2 = 12.2 +/- 4.2 min-1). The ratio of transferable amount/amount deposited appeared to indicate the depth of aerosol penetration. This increased at high respiratory frequency and tidal volume, while decreasing with increasing aerosol particle size. Potential applications of the model are discussed in the light of these results.


The mammalian thyroid gland is composed of 2 distinct endocrine cell populations concerned with the synthesis of 2 different classes of hormones. Follicular cells secrete the metabolically active iodothyronines whereas the C-(parafollicular) cells are concerned with the production of calcitonin, a hormone that influences blood levels of calcium and phosphorus, and bone cell metabolism. The synthesis of metabolic thyroid hormones is different than in other endocrine glands because the final assembly of hormone occurs within the follicular lumen. This extracellular synthesis of thyroid hormones is made possible by thyroglobulin, a glycoprotein synthesized by follicular cells. The secretion of thyroid hormones under the influence of pituitary thyrotrophin (TSH) from stores in the luminal colloid is initiated by elongation of microvilli and formation of pseudopods. FD&C Red No. 3 is a tetraiodinated derivative of fluorescein which in lifetime studies increases the incidence of thyroid follicular cell adenomas in male Sprague-Dawley rats. The striking changes in circulating levels of thyroid hormones and morphologic evidence of follicular cell stimulation are the result of
alterations in the peripheral metabolism of thyroxine. An inhibition by FD&C Red No. 3 of 5′-deiodinase in the liver and kidney would explain the lower serum triiodothyronine (T3) levels. The pituitary, sensing the lowered circulating levels of T3, increased the secretion of thyroid stimulating hormone which resulted in the morphologic evidence of follicular cell stimulation in the long-term studies. Other xenobiotics increase the incidence of thyroid tumors in rodents by a direct effect on the thyroid gland to disrupt 1 of 3 or more possible steps in the biosynthesis of thyroid hormones. Physiologic perturbations alone, such as iodine deficiency or partial thyroidectomy, can disrupt thyroid hormone economy in rodents and, if sustained, increase the development of thyroid tumors. The wide variety of drugs, chemicals, and physiologic perturbations which increase thyroid tumor development appear to act through a secondary (indirect) mechanism to promote tumor development by causing a long-standing hypersecretion of thyroid stimulating hormone. Nodular and/or diffuse hyperplasia of C-cells occurs with advancing age in many strains of laboratory rats and in response to long-term hypercalcemia in certain animal species and human beings. Focal or diffuse hyperplasia often precedes the development of C-cell neoplasms. Radiation and the feeding of diets high in vitamin D resulting in hypercalcemia have been reported to increase the incidence of C-cell tumors in rats.


Skin sloughs and necrosis from hypertonic solutions may occur in premature infants receiving peripheral intravenous fluid therapy. A simple multiple puncture method is proposed to remove the infiltrate and prevent skin sloughs.

Extravasation is one of the common complications seen with intravenous infusion. We bring forward a case of subcutaneous mannitol extravasation, which caused swelling and multiple cutaneous bullous eruptions in the hand and forearm during craniotomy. Treatment consisting of elevation of the affected extremity and application of silver sulfadiazine ointment twice daily to the injured area was successful. The possible mechanisms relevant to extravasation and its tissue damage are reviewed and discussed. Selecting proper intravenous infusion site, using pliable catheters and frequent inspection are important steps for prevention of extravasation.

ChemID 2004 Fluorescein sodium Toxnet


Solid, polydispersed disodium fluorescein aerosols (MMDae = 1.1, 3.5, and 4.4 micron) were administered under the same respiratory regime, direct to the respiratory tracts of two beagle dogs by positive-pressure ventilation. Subsequent to aerosol administration, plasma fluorescein concentrations were determined after sampling from an indwelling cannula. The amount absorbed as a function of time was estimated from these and additional data collected from intravenous control experiments in the same animals. Fluorescein absorption from the respiratory tract was apparently a first-order process, the rate increasing directly with the bioavailable dose. First-order rate constants differed but appeared unrelated to aerosol particle size, possibly reflecting similarities in their regional deposition in the canine lung. The average value for the absorption half-lives in the dogs were 19.3 and 12.2 min, showing that even lipophobic solutes such as the fluorescein dianion, are absorbed extremely rapidly via the lung. In one dog, the rate constant for fluorescein absorption after intratracheal instillation of a solution of the disodium salt was within the range of those following aerosol administration. Possible explanations are discussed.


We report a case of non convulsive status epilepticus after an intrathecal injection of fluorescein. The clinical presentation was a confusional state--the epileptic origin of which was confirmed by the electroencephalogram. This rare and relatively benign
complication should not bring about worry concerning the fluorescein test used for the
diagnosis of a dural defect and the identification of the site of a CSF leak.

**Coscas, et al. 1982.** [Incidents and accidents in fluorescence angiography]. *Annee

**Crawford Hydrology Laboratory 2004.** Dyetracing.com. *Center for Cave and Karst
Study in association with Western Kentucky University.*
[http://www.dyetracing.com/dyetracing/dy01001.html]

**Crock. 1974.** Fluorescein stereo angiography: Melbourne University technique.

123(5): 694-696.
PURPOSE: To report three cases of phototoxic reactions to intravenous fluorescein for
retinal angiography and to describe provocative testing in a volunteer. METHODS: Three
patients with phototoxic reactions were interviewed, and one volunteer underwent a
controlled challenge test by applying a potent sunscreen and exposing skin areas to direct
sunlight before and after fluorescein administration. RESULTS: All patients experienced
marked cutaneous erythema, edema, and pain to sun-exposed areas within 1 hour of
exposure. The reaction faded during a variable period of time, and one case resulted in
mild epidermal desquamation and prolonged discomfort. We noted minimal skin changes
in the volunteer who was exposed to the sun before fluorescein administration; however,
marked blanching erythema and pain were noted after fluorescein administration and
sunlight. CONCLUSIONS: Consistent with its in vitro properties as a photodynamic dye,
fluorescein may rarely act as a phototoxic agent in humans at doses employed for
fluorescein angiography.

**Davies, et al. 2003.** Extravasation and tissue necrosis secondary to central line infusions.
*Anaesthesia.* 58(8): 820-821.

**de Blecourt, et al. 1996.** [Treatment of extravasation of intravenously administered

**Deglin et al 1977** Acute myocardial infarction following fluorescein angiography. *Heart Lung*. 6(3):505-9

A 64-year-old woman with diabetes mellitus as well as hypertensive retinopathy developed an acute myocardial infarction and hypertensive crisis following the injection of 5 ml. of 10 per cent sodium fluorescein for fundus angiography. This is the first time this complication has been documented. Possible mechanisms for such an occurrence are discussed. Recommendations for recognizing and dealing with patients at high risk for cardiovascular complications of fluorescein angiography are emphasized.


Intravenous (IV) phenytoin sodium in small volumes of normal saline was administered in a municipal hospital emergency department for treatment of convulsions in 200 patients. A total of 72 complications developed in 51 patients. Twenty-nine complications were burning pain at the IV site, and 36 were related to excessive total dose of phenytoin and resultant drug intoxication. Seven other patients had cardiovascular complications, including hypotension and arrhythmias. These seven complications were related to high concentrations of drug administered at a rapid rate. Both the IV and cardiovascular complications promptly resolved when the IV rate was slowed or temporarily stopped. No patient died, and none was hospitalized because of a complication. The authors propose specific guidelines for the safe administration of IV phenytoin.


OBJECTIVE: Fluorescein is widely used in ophthalmology. Side effects related to fluorescein occur frequently but are usually benign (nausea, vomiting, lipothymia). Severe side effects are rare. We report a case of anaphylactic shock due to local application of fluorescein. CASE REPORT: A 70-year-old woman was treated for ocular conjunctivitis with local application of fluorescein. Cardiac arrest occurred due to anaphylactic shock. Resuscitation was successful. DISCUSSION: The gravity of certain complications related to the use of fluorescein underline the importance of adequate resuscitation material and adapted treatment.

Systemic antihistamines were administered prior to dye injection in 50 patients undergoing fluorescein angiography. The patients were monitored for side effects. Venous blood samples were obtained before and at three, ten and thirty minutes after intravenous administration of sodium fluorescein and analyzed for histamine levels. Three patients (6%) developed minor side effects of nausea or dizziness; this compares to an incidence of 21% in a previous series of patients from our institution untreated with antihistamines. A three-fold increase in plasma histamine levels occurred in 28% of patients following fluorescein and antihistamine injection; this compares with a 26% incidence of increase in plasma histamine in patients receiving fluorescein without antihistamines (as determined in a previous study). Prophylactic antihistamines should be considered in patients undergoing fluorescein angiography if they have a history of previous allergies or side reactions during prior fluorescein studies. However, complete prophylaxis against severe side reactions to fluorescein injections is not assured with antihistamines.


Three patients developed cellulitis and skin necrosis following fluorescein dye extravasation. This experience prompted a survey of the Macula Society membership to determine whether this complication of fluorescein angiography is as rare as the paucity of cases in the literature suggests. In addition, the manufacturer was asked to reexamine the dye lot to determine whether an impurity had been introduced unintentionally during the manufacturing process. No impurity was found in the dye lots tested. The survey disclosed only nine additional cases of skin necrosis, leading to the conclusion that skin necrosis probably represents a rare, idiosyncratic reaction. Although fluorescein angiography remains a safe procedure, efforts should be directed toward prevention of dye extravasation. When extravasation does occur, prompt and proper medical attention with close follow-up study may minimize the likelihood of skin necrosis.


Extravasations are a matter of concern in cytostatic treatment. They may range from patients' discomfort up to severe complications such as necrosis and amputation. Cytotoxic drugs in general differ in a broad variety in their ability to induce severe cutaneous reactions and therefore the possible counter-measures vary. Though the compliance with regulations concerning the application and injection or infusion of cytotoxic substances can minimize the risk of inducing an extravasation, these basic
safety procedures are reflected beside an overview of the literature concerning specific antidotes and procedures.


PURPOSE: Ocular side effects attributable to intravenous fluorescein dye are not well characterized. The purpose of this report was to describe three patients with an unusual ocular reaction after the intravenous administration of fluorescein dye. METHODS: Retrospective review of the clinical and photographic records of three patients. RESULTS: Each patient had some type of preexisting ocular inflammatory disease. Each patient described the subacute onset of a unilateral burning sensation and tearing several minutes after the administration of intravenous fluorescein dye. Findings included a new onset of or a worsening of unilateral conjunctival chemosis and injection in all three patients and yellowish discoloration of the conjunctiva in two patients. In each patient, the noninflamed (fellow) eye did not develop any symptoms or show any visible reaction. The symptoms and findings resolved promptly in the affected eye without specific treatment or effect on vision. CONCLUSIONS: Ocular side effects of intravenous fluorescein dye can include transient symptomatic burning and tearing associated with conjunctival chemosis, injection, and yellowish discoloration. Eyes with active inflammatory diseases may be predisposed to this rare effect through an unclear mechanism.


Males react adversely more frequently than females to intravenous fluorescein angiography, as shown in a study of 547 patients. Approximately 10% of all cases reacted: 12.8% of the male patients and 7.3% of the female patients had adverse responses. Nausea was most common; vomiting was infrequent, and urticaria rare (1.1%). Ten males as opposed to one female reacted markedly. More serious reactions did not occur during the 7 year testing period. No apparent cause for the increased frequency in the male cases was found.


Doxorubicin and epirubicin are strong antineoplastic agents widely used in chemotherapy. One major complication of their use is skin sloughing after subcutaneous extravasation, the degree of which is often underestimated. Both drugs have a tendency to produce liquefying necrosis in soft tissue and chronic ulcers if extravasation occurs. Three cases of extravasation, their surgical treatment and final results are presented. In cases of doxorubicin and epirubicin extravasation it is very important to perform an early extensive surgical debridement with delayed closure to avoid long hospitalization and disabling results.

Paclitaxel is an antineoplastic agent derived from the bark of the Pacific yew tree that has activity against many tumors including breast and ovarian carcinomas. In the past, its extravasation quality has been considered to be a local irritant; however, recent reports suggest that the agent may be a vesicant. A patient experienced a delayed vesicant reaction to a paclitaxel extravasation that resulted in severe necrosis. No acute symptoms were reported at the time of extravasation from the 24-hour peripheral paclitaxel infusion. However, on day 11 the patient complained of severe and progressive pain at the site of extravasation. The site was erythematous and had areas of central necrosis requiring debridement and closure by a plastic surgeon. Because paclitaxel possesses vesicant characteristics, health care professionals should be aware of its potential extravasation hazard. Prolonged peripheral infusions should be avoided or administered with extreme caution.

A 64-year-old white man with no history of cardiac or bronchopulmonary disease developed acute pulmonary edema shortly after undergoing diagnostic intravenous fluorescein angiography. The patient responded quickly to a course of oxygen, positive pressure breathing, diuretics, and sedation.


**HSDB 2003 Fluorescein**  
*Hazardous Substances Databank TOXNET*  

A 23-year-old white man experienced burning pain up his right forearm while receiving phenytoin intravenously in the dorsal wrist. Swelling occurred, followed a few days later by an erythematous eruption that eventuated in superficial skin sloughing. The histopathology of two right forearm biopsies, taken a few days apart 3 to 4 weeks after the infusion, was characterized by partial epidermal necrosis and frequent multinucleate keratinocytes. Localized cutaneous reactions to phenytoin and the occurrence of multinucleate epidermal cells in inflammatory skin disease are reviewed.

To detect cystoid macular edema after extracapsular cataract extraction, the authors used indirect ophthalmoscopy after oral application of fluorescein, rather than intravenous fluorescein angiography. The patients drank 10-20 ml 10% fluorescein sodium in 250 ml orange juice. Ophthalmoscopy was performed 30-45 minutes later using an exciter filter. Twenty-five patients with a tentative clinical diagnosis of cystoid macular edema were examined in this way. In six of them a manifest edema was detected. The results were confirmed by intravenous fluorescein angiography.

**Ikezawa, et al. 1992.** Enhancing effects of fluorescein on beta-lactam rash. II: Enhancing effects of fluorescein on generalized rash induced by beta-lactam antibiotics in guinea pigs.  
*J.Dermatol.* 19(9): 537-543.  
Healthy volunteers, who were receiving intravenous injections of cefclidin (CFCL) with frequent concomitant use of fluorescein (F) and oxybuprocain (O) in the eyes for measurement of ocular tension, developed drug eruptions at the high frequency of 66.7%. The injection of CFCL alone induced the eruptions at an incidence of 2.8%. The cause of this high eruption rate was thought to be the simultaneous treatment with F and/or O. Therefore, we conducted experiments with CFCL-induced generalized rash (GR) in guinea pigs. Guinea pigs treated with F and O during both the phases of immunization and intraperitoneal elicitation developed CFCL rashes at a high frequency. This CFCL-rash was augmented by the treatment with F during either phase, but not by the treatment with O. Skin testing induced delayed type hypersensitivity (DTH) reaction to O in some
animals, but the DTH to F was not induced in animals immunized with F in complete Freund's adjuvant. Furthermore, F augmented rashes induced not only by CFCL but also by other beta-lactam antibiotics such as cefsulodin and sulbenicillin. Accordingly, it is likely that F played a dominant role in the high incidence of drug eruptions during the volunteer trials with measurement of ocular tension.


Ceftazidime has been evaluated in a total of 1548 cases of infection involving medical and surgical patients. Most of the cases were treated with 1 to 2 g/day. Of the total number of assessable cases (1418), over 80% responded satisfactorily (1141). Bacterial eradication was achieved in 850 cases (81% of those assessable). The incidence of adverse events was low (2.1%) being observed in 32 cases out of 1529 that were assessable. Clinical events were mainly skin eruptions, nausea and vomiting. Laboratory abnormalities were mainly slight elevations of serum GOT, GPT, alkaline phosphatase and eosinophil counts.


The revelation that intravenous sodium fluorescein is not all that it might seem to be may be a significant finding in the light of the adverse reactions to fluorescein that have been previously reported. Analysis of commercially prepared intravenous sodium fluorescein by mass spectroscopy and nuclear magnetic resonance has indicated that an industrial solvent used in the manufacturing process has not been eliminated. Dimethyl formamide is an industrial solvent with a maximum acceptable exposure level of 10 parts per million for dermal contact. It has been found in quantities of 5000 parts per million in the fluorescein for intravenous use. This investigation was prompted by a significant increase in the adverse reactions in patients receiving intravenous fluorescein in the retinal photographic unit at the Manchester Royal Eye Hospital.


PURPOSE: To evaluate the belief that the frequencies of contrast material extravasation and minor, nonidiosyncratic contrast material reactions correlate with intravenous injection rates. MATERIALS AND METHODS: Complications of 6,660 consecutive injections of contrast material for computed tomography were prospectively recorded. Ionic (n = 4,851) or nonionic (n = 1,809) contrast material was injected at 0.5-4.0 mL/sec. The injection rate was 1.9 mL/sec or less in group 1 (n = 2,899), 2.0-2.9 mL/sec in group 2 (n = 2,475), and 3.0-4.0 mL/sec in group 3 (n = 1,286). RESULTS: The
extravasation rate (0.6%) did not differ significantly between the groups. The reaction rate (8.4%) also did not differ significantly between the groups. The rate of minor reactions (8.0%) was higher with ionic (9.9%) than nonionic (2.9%) contrast material (relative risk = 3.4). The rate of major reactions (0.4%) did not vary significantly with type of contrast material. The rate of nausea or vomiting (3.8%) did not differ significantly between the groups but was higher with ionic (4.9%) than nonionic (1.1%) contrast material (relative risk = 4.5). The rate of severe warmth (2.1%) was significantly higher in group 3 (2.8%) than group 1 (2.0%) or 2 (1.8%). CONCLUSION: No correlations exist between injection rate and extravasation rate or overall reaction rate.


BACKGROUND: Fast sequence retinal fluorescein angiography is a commonly employed diagnostic procedure within the optometric practice with relatively few serious adverse reactions. A retrospective study was conducted to document the incidence of adverse reactions with this procedure. METHODS: A total of 1,173 patient charts who had undergone intravenous injection for retinal fluorescein angiography at a specialty referral clinic or a referral clinic at a school of optometry. All patients had been intravenously injected with 500 mg of sodium fluorescein in 25% or 10% solution. Adverse reactions were noted within the charts. RESULTS: The most common adverse reaction were nausea (.8% of patients) and urticaria (.6% of patients), with other reactions including emesis and hypoglycemia. Extravasation of dye was noted in .2% of patients. No acute anaphylaxis was noted. CONCLUSIONS: Fast sequence retinal fluorescein angiography is a relatively safe diagnostic test. However, one should be prepared to handle acute anaphylaxis within the office before administering the test because of previously published cases of life-threatening reactions.


Sodium fluorescein solutions, 3 ml of 25% solution and 5 ml of 10% solution, were compared with a double-blind crossover method in a group of 41 normal volunteers and in a group of 42 patients who had diverse ophthalmic disorders. Following injection of the solutions into the antecubital vein, visualization, serial fluorescein angiograms, and five-minute phase angiograms were studied and compared. The untoward reactions reported in both studies were of types usually associated with sodium fluorescein, the most common of which was a mild, transient nausea. On the basis of our results, there is
no significant difference in the incidence and severity of adverse reactions between the 10% and 25% solutions. In the volunteer study, the 25% solution was significantly superior in visualization and paired comparison (P less than .001) in the patient study, the 25% solution was significantly superior in angiogram quality (P less than .01), five-minute phase angiogram (P less than .05), and paired comparison (P less than .005). The overall superiority of the 25% concentration in a 3-ml volume was demonstrated both subjectively and objectively in the volunteer study and in the patient study.


Kahn, et al. 2002. Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. Crit.Care Med. 30(8): 1899-1901. OBJECTIVE: To describe a case of severe skin necrosis resulting from peripheral intravenous administration of low-dose vasopressin in a patient with catecholamine-resistant septic shock. DESIGN: Case report. SETTING: Medical intensive care unit at the University of Chicago, Chicago, IL. PATIENT: A 46-yr-old female with ventilator-dependent, proliferative-phase acute respiratory distress syndrome complicated by Pseudomonas aeruginosa bacteremia and sepsis. MEASUREMENTS AND MAIN RESULTS: A patient recovering from acute respiratory distress syndrome developed septic shock from Pseudomonas aeruginosa bacteremia while in the medical intensive care unit. Vasopressin (0.04 units/min) was administered through a peripheral venous catheter for hypotension unresponsive to exogenous catecholamines. The patient subsequently developed severe ischemic necrosis of the skin and soft tissue surrounding the catheter site. The vasopressin was stopped, and the skin lesion progressed to bullae formation with extensive superficial erosion. CONCLUSIONS: Peripheral administration of low-dose vasopressin for septic shock should be discouraged because of the risk of ischemic skin complications.

Karhunen, et al. 1986. Adverse reactions to fluorescein angiography. Acta Ophthalmol.(Copenh). 64(3): 282-286. Adverse reactions to ophthalmic patients during 9909 fluorescein angiographies during 9 years were registered. Nausea (4.6%) and vomiting (1.3%) were the most common untoward reactions. Allergic skin manifestations occurred in 48 patients, and 5 patients complained of shortness of breath. 56 patients (0.6%) felt dizzy during or immediately after the investigation. Nine patients complained of chest pain, three of whom developed myocardial infarction. Sixteen patients collapsed during the procedure. One healthy male, 42-year-old, collapsed after the injection of fluorescein during angiography, and electrocardiogram showed an asystole of 24 seconds. Otherwise, the electrocardiograms
registered on 100 consecutive patients did not reveal any systematic changes in heart rate or rhythm during fluorescein angiography.


BACKGROUND: Localization of dural fistulas in the region of the anterior or lateral skull base may be difficult. For many years, a sodium fluorescein solution of 0.5 to 5% (2.5-50 mg) has been administered intrathecally by way of the lumbar space. However, fluorescein is not commercially available for this stated purpose in either Germany or the United States. METHODS: Retrospectively, 420 fluorescein applications by the authors were retrospectively analyzed. Under the Freedom of Information Act, the United States Federal Drug Administration and the manufactures of fluorescein were queried for adverse reaction reports. RESULTS: Four hundred twenty fluorescein applications in 305 patients could be evaluated. Mean age of recipients was 46.9 years, ranging from 1 to 82 years. At a concentration of 5% fluorescein, 26 patients on the day of surgery and 69, 37, 34, and 14 patients on days 2 through 4 suffered from minor side effects that may or may not have been related to this drug. Two of these patients had grand mal seizures, which were attributable to simultaneous intrathecal application of contrast medium. All other side effects were thought to be the result of a postspinal headache and related lumbar puncture. At a concentration of 0.5%, the intraoperative intrathecal administration of 0.5 to 2 mL of fluorescein followed by 4 to 5 days of lumbar drainage resulted in some degree of spinal headache without other complications. In both groups, no patient had sequelae longer than 4 weeks. An additional seven complications were reported to the Federal Drug Administration and the fluorescein manufacturers at doses of 100 to 700 mg. CONCLUSIONS: Complications from intrathecal application of fluorescein appears to be dose dependent. At concentrations of 5%, or preferably lower, side effects are transient. A grand mal seizure can be minimized when following the general cautions of lumbar puncture and dose. The patient should be supervised for 24 hours. A written informed consent from patients for use of fluorescein is recommended.


Fluorescein angiography is a safe, well-standardized procedure for establishing fundus abnormalities. It facilitates documentation of the finest detail of the fundus, allows
estimation of the blood flow through the retina, and permits the doctor to evaluate the integrity of the retinal vessels. When there is good communication between doctor and patient, and between doctor and photographer, it is an especially useful procedure.

**Kelly, et al. 1989.** Convulsion following intravenous fluorescein angiography. 
Tonic-clonic seizures followed intravenous fluorescein injection for fundus angiography in a 47-year-old male. Despite precautions this adverse reaction recurred on re-exposure to intravenous fluorescein.

A patient receiving intraperitoneal chemotherapy with cisplatin and cytosine arabinoside developed an abdominal skin rash similar in appearance to Cullen's sign. She subsequently received intraperitoneal mitoxantrone, which became visible in the skin close to the peritoneal catheter tract in the region of the skin rash within 24 hours of drug administration. There was no evidence for drug extravasation from the entry portal of the peritoneal catheter or visible fluid leakage. Although the clinical picture was dramatic there was no significant clinical sequela to the extravasation of these drugs. The potential significance of this event is discussed.


This report describes a novel technique for screening potential carcinogens and mutagens. The DNA-cell-binding (DCB) assay is based on earlier observations which indicated that DNA and other nucleic acids exposed to active carcinogens strongly react with other macromolecules, producing nucleic acid--nucleic acid and nucleic acid--protein adducts. The latter group of adducts included complexes with proteins present in both prokaryotic and eukaryotic cell membranes. Increased attachment of DNA to the intact bacterial and animal cells was seen in the presence of active carcinogens or carcinogens activated by extracts from mouse and rat livers. We have conducted a survey of almost 280 chemicals including 130 with known carcinogenic potential (i.e., either known carcinogens or known non-carcinogens). The DCB test and animal assays agreed in about 96% of cases. Thus, as a predictor of potential carcinogenicity, this assay compares favorably with other rapid methods currently in use. In this respect, the DCB assay is also superior to other
techniques which measure the formation of macromolecular complexes, such as velocity centrifugation through sucrose gradients, gel electrophoresis, filtration through nitrocellulose filters, chromatography on methyl-esterified albumin, equilibrium density gradient centrifugation, etc. In the few cases for which the data were available, combining the results of DCB assays with the results of experiments in which the induction of DNA--protein adducts in living human cells in tissue culture has been measured by cold phenol extraction, the predictability was increased to 100%. We suggest that DCB assay should be used either alone or in combination with other rapid methods of carcinogen detection for screening industrial, environmental and other chemicals and chemical mixtures for their carcinogenic potential. Ways of further improving and simplifying the DCB tests are considered.


Intravenous fluorescein angiography is a commonly performed and extraordinarily valuable diagnostic procedure. The frequency of adverse reactions after angiography has varied considerably in previous reports. In a prospective study of 2789 angiographic procedures in 2025 patients, the authors found that the percentage of adverse reactions depended strongly on the patient's angiographic history. Overall, adverse reactions followed 4.8% of the angiographic procedures. These reactions included nausea (2.9%), vomiting (1.2%), flushing/itching/hives (0.5%), and other reactions (dyspnea, syncope, excessive sneezing) (0.2%). No cases of anaphylaxis, myocardial infarction, pulmonary edema, or seizures occurred. The percentage of reactions was 1.8% for patients who had had previous angiography without ever having had an adverse reaction. In contrast, the percentage of reactions was 48.6% for patients who had had an adverse reaction to angiography previously.


This experimental study in the rabbit establishes a reliable model for the production of skin necrosis analogous to intravenous extravasation injuries in humans. The effectiveness of hyaluronidase in reducing the extent of tissue injury is examined, using several different toxic agents.

Sodium fluorescein is an organic dye widely used as a diagnostic aid. This article reports a case of a photosensitivity reaction associated with intravenous administration in a healthy volunteer. To our knowledge, this is the 1st case of a photosensitivity reaction of the immediate type due to fluorescein reported in the literature, which probably indicates its very low incidence. The literature on photosensitization to fluorescein is reviewed.


FD&C Red No.3 (erythrosine) has been used as a dye in foods, drugs and cosmetics since its approval by the US Department of Agriculture in 1907. In 1977 the Certified Color Manufacturers' Association (CCMA) initiated studies on FD&C Red No.3 including chronic toxicity and carcinogenicity studies in rats and mice. Data from the CCMA chronic studies revealed an increased incidence of thyroid follicular cell hyperplasia and adenomas in male rats that received 4% FD&C Red No.3 in the diet (2464 mg/kg/day) during life-time (30 months) following in utero exposure. In this report, results of published studies on the mutagenicity of FD&C Red No.3 are critically reviewed. Additional mutagenicity tests including Ames Salmonella/microsome assay, L5178Y TK+- mouse lymphoma assay, mouse micronucleus test and mitotic recombination assay with yeast Saccharomyces cerevisiae strain D5 are described. These test results together with the literature review indicate that FD&C Red No.3 can be considered non-mutagenic across several genetic endpoints including gene mutation, chromosome aberrations, primary DNA damage and cell transformation. The results of the genotoxicity assessment generally exclude FD&C Red No.3 as a genotoxic initiator and suggest that some other mechanism is responsible for the increase in tumors.


Nausea and vomiting have not been clearly associated with parenteral acyclovir. We report a pediatric patient who developed nausea and vomiting apparently associated with intravenous acyclovir therapy. The child received acyclovir (1500 mg/m2/d) for treatment of recurrent varicella zoster with possible dissemination. Nausea and vomiting could be attributed only to acyclovir therapy. Discontinuing the drug resulted in a resolution of the adverse symptoms. Adverse effects of parenteral acyclovir can mimic the early manifestations of Reye's syndrome, which is an important consideration in children with viral infections. It is necessary to distinguish the cause of nausea and vomiting for proper management of patients.


The authors investigated physical and chemical properties of fluorescein, a substance widely used in ophthalmology. In view of the increased application of fluorescein angiography in the diabetological programme, the authors draw attention to possible undesirable effects of fluorescein and submit an account of complications recorded after application of this substance to 576 patients examined by this method at the Ophthalmological Clinic in Brno.


We examined whether a prick test was a valuable method in comparison with an intradermal skin test for predicting an anaphylactoid reaction to intravenous injection of fluorescein solution. Fifteen hundred cases were tested. The number (rate) of positive reactions to the prick test with 10% and 1.0% fluorescein solution was 2 (0.1%) and 0 (0.0%), respectively. In contrast, positive reaction to the intradermal skin tests with 10% and 0.1% fluorescein solution was observed in 686 cases (45.7%) and 13 cases (0.9%), respectively. Fluorescein angiography (FAG) was performed in 1,499 of the 1,500 cases. Adverse reactions such as nausea, cough, cold sweat, urticaria, and shock were noted in 85 cases (5.7%). Typical anaphylactoid shock occurred in one case (0.07%), which was one of the two cases positive to the prick test with 10% fluorescein. In the other positive prick test case, FAG was cancelled because of the high probability of anaphylactoid

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shock. The results suggest that a prick test with 10% fluorescein solution can markedly cut down the false positive reactions and can be a useful test for the prospective diagnosis of anaphylactoid reactions to intravenous fluorescein administration.


Pregnant rabbits in their first and second "trimesters" of gestation were used in a controlled study to evaluate the teratogenicity of fluorescein sodium. Injections of the drug were given in doses comparable to those planned for human administration. No abortions or defects apparent at birth or as delayed manifestations were evident as a result of the drug therapy


PURPOSE: A prospective survey was undertaken to investigate ethnic variations in the frequency of nausea and vomiting after fundus fluorescein angiography (FFA).

METHOD: Between May and September 1998, 197 adult patients were recruited to the study. A questionnaire containing closed-ended questions was completed by nurses after each FFA and a questionnaire was given to patients to complete 5 hours after the procedure at home. Patients' anxiety level was measured before FFA using a 5-item ordinal response scale. RESULTS: Results indicate that patients from black, Asian, Chino-Asian and mixed ethnic origins are significantly more likely to vomit and feel nauseous immediately after the administration of fluorescein dye. Patients with a history of nausea after FFA are significantly more likely to feel nauseous again after repeat FFA. CONCLUSION: Ethnic origin and a previous history of nausea and vomiting appear to be important factors in FFA-induced nausea and vomiting. The results of this study have led the investigators to develop a protocol for the prophylactic treatment of nausea and vomiting following FFA.


This report describes two cases of grand mal seizures following intrathecal injection of fluorescein to delineate CSF-leakage. Recurrent phases of apnea necessitated artificial ventilation in one case. The results of CSF and serum investigations are discussed as well as EEG and EMG findings. As fluorescein has proved to be a potentially epileptogenic drug, its use for patients with a past history of seizures should be very carefully considered. All patients having received intrathecal fluorescein should be kept under observation for at least 4 to 6 hours.


We have performed Retinal Fluorescein Angiograms in three groups of patients who had been previously administered, respectively: intravenous sodium fluorescein, hard gelatin-coated fluorescein oral capsules, and enteric-coated fluorescein capsules. In all groups, we carried out a curve of the dye plasma levels. We concluded that the enteric-coated fluorescein capsules provide effective dye plasma levels for the performance of the angiogram between 40 and 60 minutes later, thus obtaining great sharpness and quality retinal images, much better than those attained with the hard gelatin-coated fluorescein capsules.


Fluorescein angiography is a routine procedure in ophthalmology. There can, however, be some harmful side-effects from fluorescein injections. It is important that all personnel involved in using this investigative procedure should be aware at all times of the possible side-effects and be ready to detect and control any adverse reaction. A case presentation is given of a 40-year-old man who had an unusual reaction to fluorescein resulting in carpopedal spasm.


Skin necrosis from intravenous infiltration of soft tissue is a rare but potentially devastating complication of intravenous therapy. Vinca alkaloids are among the intravenous drugs with the highest destructive power. We report two cases of skin necrosis from accidental extravasation of vinorelbine, a semisynthetic analogue of vinblastine, rarely described as being responsible for this event. Histopathologic study showed separation of the dermis from necrotic epidermis, associated with cytologic atypia, in both patients, and focal necrosis of eccrine glands in one of them. We consider that intravenous infusions of vinorelbine should be performed using the preventive measures and care applied for other chemotherapeutic agents with high potential for induction of skin necrosis due to extravasation.


Intravenous fluorescein is frequently used to assess tissue perfusion and predict flap viability, although its safety has recently been questioned due to cardiovascular side effects. Vital signs of 50 patients who received fluorescein were monitored by anesthesiologist to assess flap viability. Blood pressure readings were recorded at 5-minute intervals for at least 1 hour before and after fluorescein administration. Repeated measure analysis of variance was performed to determine any significant sustained (greater than or equal to 30 minutes) or transient (less than or equal to 15 minutes) differences in pressure changes after fluorescein administration. No significant (p less than or equal to 0.1) differences in pressure were noted for any identifiable group of patients. Minor reactions included transient nausea with no vomiting (5), sustained blood pressure increases of greater than 10% preadministration values (9), transient pressure drops of greater than 10% (10), and sustained pressure drops of greater than 10% (4). These 4 patients responded to increased fluid therapy without need for pressor agents.

The authors describe a case in which 0.5 cc of 5% fluorescein diluted in 10 cc of cerebrospinal fluid (CSF) was injected at the L4-5 level for evaluation of nasal CSF leakage. Within minutes, tone increased in lower extremities accompanied by knee and ankle clonus and subjective numbness up to the waist. Non-preserved saline irrigation of the lumbar CSF was administered until it became clear, and the patient's head was elevated to retard the developing symptomatology. Although a transient temperature elevation was observed with negative CSF cultures, all signs and symptoms cleared within 48 hours. In a survey of the members of the American Association of Neurological Surgeons regarding frequency of use and complications stemming from intrathecal fluorescein, the response rate was 58.3% (1111) of the 1907 members, of which 6.8% (76) had used intrathecal fluorescein, and among those, 25% (19 of the 76) had observed complications involving lower extremity weakness, numbness, generalized seizure activity, opisthotonos, and cranial nerve deficit. No complications were permanent. The authors recommend caution if intrathecal fluorescein must be used. Means should be available to clear the CSF of the agent and elevate the head if complications arise.


A 49-year-old woman presented with a hemoglobin level of 9.5 g per dL (95 g/L), reticulocyte count of 6.7 percent (0.067), and hemoglobinuria. The next day, the hemoglobin had dropped to 5.8 g per dL (58 g/L), and total bilirubin was 8.8 mg per dL (150 mumol/L). The serum reacted 2+ with all red cells (RBCs). The direct antiglobulin test (DAT) was 3+ with anti-IgG and 1+ with anti-C3, but eluates prepared by two different methods did not react with untreated RBCs. The eluate reacted 2+ with amoxicillin-coated RBCs; amoxicillin had been listed in the patient's record as a previous medication. The patient denied recent ingestion of amoxicillin. Further investigation documented the injection of a dye, fluorescein sodium (AK-FLUOR-25%), for an ophthalmologic fluorescein angiographic study 2 days before admission. RBCs coated with AK-FLUOR reacted with the eluate. Controls consisting of normal serum, an eluate prepared from DAT-negative RBCs, and a serum known to contain anti-penicillin did not react with AK-FLUOR-coated RBCs. Nine days later, the DAT was negative and the serum did not react with untreated RBCs. In the presence of AK-FLUOR (1-in-125) or amoxicillin (1 mg/mL), the serum reacted 2+ in the antiglobulin test. Antibodies to AK-FLUOR and amoxicillin appeared to react by two mechanisms, which is similar to results in recent reports of other drugs associated with hemolytic anemia. AK-FLUOR has not previously been reported to be associated with hemolytic anemia.

**Myata et al 1972** [Toxicology of fluorescein] *Nippon Ganka Gakkai Zasshi*
76(12):1601-7

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To determine the effects on the pulmonary barrier of several surface active agents, a series of metered dose inhalers (MDIs) was prepared and used to dose aerosolized surfactant to the airways of isolated perfused rat lungs. The MDIs contained a range of concentrations, from 0.1 to 5.0% (w/w), of either oleic acid, oleyl alcohol, or Span 85, which released approximately 45 micrograms (0.1%, w/w) to approximately 1660 micrograms (5.0%, w/w) of surfactant per actuation. The permeability of the pulmonary barrier was assessed by the rate of transfer of disodium fluorescein dosed as 100 microliters of aqueous solution (1 mg/ml) after administering the surfactants. Some 12.1 +/- 4.7% of the recovered surfactant, per dose, was assessed to reach the pulmonary regions of the lung. All surfactants tested caused an increase in fluorescein transfer rates. A single actuation from the MDI containing 5% (w/w) oleic acid produced gross edema in all lungs tested within 40 min and the first-order half-lives of absorption were reduced almost threefold, from 12.9 +/- 2.5 min for controls to 4.5 +/- 0.8 min. Differences in absorption were noted between the acid and the alcohol, which is consistent with the hypothesis that both the hydrocarbon chain and the polar head group have roles in the altered permeability to fluorescein. The absorption of fluorescein when dosed from the MDI containing 5% (w/w) Span 85 was increased but all surfactants dosed from the lowest concentration MDI of 0.1% (w/w) did not alter absorption rates of the dye relative to those of controls. Results are discussed in light of current interest in absorption enhancement and the presence of surfactants in currently marked MDIs.

Noppen et al 2004. Fluorescein-enhanced autofluorescence thoracoscopy in primary spontaneous pneumothorax. *Am J Respir Crit Care Med.* 170(6):680-2. The exact site of air leakage in a patient with primary spontaneous pneumothorax is difficult to determine and locate. In particular, the role of rupture of emphysema-like changes (blebs and bullae) versus that of enhanced porosity of lung parenchyma in the pathophysiology of primary spontaneous pneumothorax remains unclear. This is the first description of a patient with recurrent primary spontaneous pneumothorax in whom inhalation of aerosolized fluorescein followed by autofluorescence thoracoscopy allowed in vivo localization of various lung areas of extensive subpleural fluorescein accumulation which were not, or only partly, visibly abnormal during normal white light thoracoscopy. No air leak was present at the time of thoracoscopy. No emphysema-like changes were seen. Our findings suggest substantial areas of parenchymal abnormality that remain unnoticed.
by white light thoracoscopic inspection of the parenchymal surface. In this respect, fluorescein-enhanced autofluorescence thoracoscopy may become an exciting tool in the study of the pathophysiology of primary spontaneous pneumothorax, and could prove useful in clinical practice in determining the sites of surgical staple resection whenever this treatment modality is considered.


In this review of recent articles on ocular toxicology, the author concentrates on undesirable effects on the eye induced by systemically used xenobiotics. These effects include increased tear flow elicited by systemic cyclosporine; uveitis associated with inactivated influenza vaccine, intravenous immunoglobulins, or skin tattoos; iritis associated with intravenous streptokinase; corneal epithelial erosion associated with the use of an alcohol-based antimitting spray; decreased color vision associated with workplace exposure to perchloroethylene, or to digoxin; myocardial ischemia induced by topical atropine; and systemic exposure to cyclopentolate after topical instillation. Ocular irritation associated with systemic use of 5-fluorouracil may be attenuated with prophylactic ice packs. At doses evaluated for treatment of choroidal neovascularization, systemic alpha interferon leads to toxicity in multiple organ systems. Promethazine precipitates when injected into intravenous lines with fluorescein. No drug achieves ultimate efficacy or ultimate safety. Thus, the decision to employ a given therapy involves a physician's evaluation of its therapeutic index-the ratio between efficacy and toxicity.


Treatment of pulmonary and systemic diseases may be improved and toxicity reduced by pulmonary deposition of drug-containing aerosols exhibiting delayed dissolution. Aqueous disodium fluorescein and pentamidine aerosols were dried, concentrated, and condensation coated with paraffin wax. The apparent mass median aerodynamic diameters of the coated fluorescein particles were 2.8-4.0 microns. Wax-to-fluorescein ratios were 0.38-1.05. The dissolution half times determined using a single-pass flow system were 1.5 min for uncoated fluorescein and 0.8 min for uncoated pentamidine. These increased over threefold when the aerosols were coated with paraffin wax to maxima of 5.3 and 2.6 min, respectively. Wax-coated aerosols generated from fluorescein mixed with 99mTc-labeled iron oxide colloid delivered to the canine lungs
demonstrated a 3.4-fold increase in the absorption half time of disodium fluorescein compared with uncoated fluorescein (11.2 vs. 38.4 min). The absence of changes in pulmonary function on inhalation of these wax-coated aerosols, together with a high drug load and delayed release, establishes a foundation for future therapeutic applications.


All complications were recorded from the initial 2488 cases studied with digital intravenous angiography (DIVA) at New York University Medical Center. Mechanisms of producing these reactions were categorized into procedure-related, contrast-medium-related, or disease-related. The complications included extravasation of contrast material into the arm (11 patients) and mediastinum (two), acute pulmonary edema (four), hypotension (23), thrombophlebitis (two), and grand mal seizure (one). Recommendations are made that would allow DIVA to be performed more safely.


Extravasation of intravenous phenytoin can result in serious soft-tissue complications. Three patients are presented, one of whom lost a hand. Assessment of circulation and early decompression fasciotomies may be necessary in such cases. Caution is recommended in the intravenous administration of phenytoin. Infusions at rates of less than 50 mg/min and education of nursing staff about this potential complication will decrease its incidence.


Paclitaxel is a new antimitotic derived from yew-tree, used for the treatment of ovarian and breast cancers. The local toxicity of paclitaxel is still poorly known. We report one of the first observations of accidental subcutaneous extravasation of paclitaxel. Local epidermic necrosis was observed and evolution was good with local treatment only. Treatments of such extravasation are discussed.


RTECS 2004 Fluorescein, disodium salt The Registry of Toxic Effects of Chemical 
Substances http://www.cdc.gov/niosh/rtecs/lm52c768.html

JAMA. 206(9): 2118-2119.


Sodium fluorescein (10%) when injected intravenously (5 ml/kg) in pregnant albino rats crossed the placental barrier and appeared to be distributed throughout the fetus within 15 min. It was detectable in the fetus up to 4 h after injection but not beyond 24 h. A single intravenous administration of sodium fluorescein did not produce embryotoxic or teratogenic effects. Oral LD50 studies using sodium phenobarbital on rats which received sodium fluorescein during their fetal development showed no apparent effects of sodium fluorescein on their drug detoxification systems.


Mucoadhesive, hydroxypropylcellulose (HPC) microspheres were prepared for powder inhalation and their feasibility for enhancing pulmonary drug absorption was investigated. Respirable-sized microspheres, incorporating crystalline or amorphous fluorescein (used as a model drug), were prepared by spray-drying aqueous or ethanol HPC systems, respectively. These were prepared from a variety of HPC grades (SL, L, M and H types) in different fluorescein-HPC ratios (1:1-1:10). The microspheres were administered to tracheally-intubated guinea pigs as powder aerosols and their fluorescein pharmacokinetics studied, and compared to those for pure crystalline fluorescein ('control'). All microspheres were prepared and aerosolized within a MMAD range of 1.3-2.6 microm (GSD< or =2.1). Fluorescein's dissolution was increased in the amorphous form by 6.5-fold when compared to the crystalline material (83.9-87.2 vs.
13.5 microg/ml, respectively). Poor dissolution for the 'control' crystalline fluorescein appeared to be rate-determined, which showed bi-phasic absorption profiles (T(max)=60 min), simultaneously competing with mucociliary clearance out of the lower airways. While the crystalline/HPC microspheres prolonged absorption, the amorphous fluorescein/HPC microspheres showed rapid absorption with T(max)=0 min (immediately after the administration had terminated). This was explained by enhanced fluorescein dissolution and was consistently observed irrespective of the fluorescein-HPC ratio or HPC grade. However, the microspheres with the least viscous HPC-SL and the lowest fluorescein-HPC ratio (1:1) failed to enhance bioavailability, presumably because the mucociliary clearance was undisturbed. In contrast, the microspheres with the highly viscous HPC-H with ratios > or = 1:4 successfully enhanced absorption, achieving 88.0% bioavailability by virtue of HPC increasing the dissolution and retarding the mucociliary clearance.


The new non-ionic contrast medium iomeprol (Iomerlon) 150/200/250/300/350/400 was tested in a non-selected patient population (n = 4811). The aim of the clinical testing, in a very diverse range of radiographical examinations, was to evaluate its tolerance. A high percentage of the patients showed risk factors such as allergic predisposition (22.0%), cardiovascular diseases (45.3%), and kidney disease (15.1%). In addition, high doses of the contrast medium were used, depending on the radiological problem. The proportion of patients over 70 was 19.5%. Iomeprol proved to be an extremely well tolerated nonionic contrast medium. With the exception of nausea, systemic side effects occurred in less than 1% of cases.


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The second phase of the survey of adverse reactions to contrast media was based on 4,120 case reports and involved the collaboration of radiologists in 45 institutions. It was directed primarily to a study of the distribution patterns of adverse reactions and the likelihood of recurrence of the same reaction on repetition of the examination. It was found that major life-threatening reactions involving the respiratory system are usually accompanied by minor or less serious reactions, while those involving the cardiovascular system are accompanied by the more serious reactions. Major life-threatening reactions do not usually recur on reexamination, while minor reactions tend to be repeated more often.


[http://www.nova.edu/~jsowka/fluor.html]

Paclitaxel is a novel anti-neoplastic with a wide spectrum of activity in various malignant tumors. Extravasation of chemotherapy drugs is a widely feared adverse event in oncology patients. A Medline search between 1966 and October 2002 was conducted to identify case reports related to paclitaxel extravasation, as well as a bibliography screening of identified papers. The goal of this work is to summarize the available reports of paclitaxel extravasation and assess its vesicant potential. Additionally, management strategies for extravasation events due to paclitaxel are assessed.


Skin ischemia, necrosis, and gangrene are uncommon but known complications of dopamine extravasation. In most cases, these complications are associated with the use of Contract No. IOM-2794-04-001
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high-dosage dopamine infusion. Subcutaneous phentolamine has been used as a therapeutic agent for these complications. However, this is the report of the first neonatal case report in the English literature of prompt reversal of imminent dermal ischemia and necrosis associated with low-dose dopamine infusion using subcutaneous phentolamine.


Four widely used in vitro assays for genetic toxicity were evaluated for their ability to predict the carcinogenicity of selected chemicals in rodents. These assays were mutagenesis in Salmonella and mouse lymphoma cells and chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells. Seventy-three chemicals recently tested in 2-year carcinogenicity studies conducted by the National Cancer Institute and the National Toxicology Program were used in this evaluation. Test results from the four in vitro assays did not show significant differences in individual concordance with the rodent carcinogenicity results; the concordance of each assay was approximately 60 percent. Within the limits of this study there was no evidence of complementarity among the four assays, and no battery of tests constructed from these assays improved substantially on the overall performance of the Salmonella assay. The in vitro assays which represented a range of three cell types and four end points did show substantial agreement among themselves, indicating that chemicals positive in one in vitro assay tended to be positive in the other in vitro assays.


The value of administering 25 mg of levosulpiride per os approximately one hour before the sodium fluorescein bolus used in fluorangiography is assessed in order to avoid to the onset of nausea and/or vomiting during and after the test. The study was performed in 35 patients. No nausea and/or vomiting was observed in over 90% of cases treated.


The authors have demonstrated a significant decrease of the plasmatic ionized calcium level in 84 patients during retinal fluorangiography likely due to a chemical bond between calcium and fluorescein. The side effects noticed during the procedure were similar to that quoted in the literature; their frequency, however, was not correlated with the decrease of the plasmatic ionized calcium level, even though the magnitude of the decrease was twice as great in the patients who experienced some trouble as in those who...
did not. This lack of correlation may be related to the too small patients sample. A greater frequency of side effects has been noticed in patients treated by calcium inhibitors.

**Umeda 1954** Experimental production of sarcoma in rat by injection of fluorescein sodium. *GANN* 45: 446-447

**Umeda 1956** Experimental study of xanthene dyes as carcinogenic agents. *GANN* 47: 51-78


**Venes. 1977.** The use of intravenous fluorescein in the repair of large myelomeningoceles. Technical note. *J.Neurosurg.* 47(1): 126-127. Intravenous fluorescein has been found a valuable guide in the identification of necrotic skin, which can then be debrided before wound closure. Fluorescein was used in four infants undergoing repair of large myelomeningoceles with no deleterious effects.


This is a report on the results of a national survey designed to study the nature and frequency of moderate and severe complications of intravenous fluorescein angiography. In this survey, 2434 responding ophthalmologists reported on 221,781 fluorescein angiograms performed in the year 1984. Adverse reactions were classified as mild, moderate, severe, and death, depending on the duration of the effect, the necessity for medical intervention, the time required for its resolution, and the final outcome. The frequency rate for a moderate reaction was (1:63), for a severe reaction (1:1900), and for death (1:222,000). A review of previous studies on adverse reactions to the drug, a compilation of suggested methods for the amelioration and prevention of the complications, and a comparison of the responses of the general ophthalmic public to the members of The Macula Society are also reported.

Zografos. 1983. [International survey on the incidence of severe or fatal complications which may occur during fluorescein angiography]. *J.Fr.Ophtalmol.* 6(5): 495-506.

Serious or fatal accidents during fluorescein angiography were assessed by an international survey involving answers from 260 clinics in 30 different countries in respect of 594, 687 angiographies. Incidence of fatal accidents was one case per 49,557 angiographies, and of serious accidents, one case per 18,020 angiographies. The total number of accidents reported was 45 cases, equal to one case per 13,215 angiographies. Age, general health of the patients, and the experience of the different clinics who perform this examination, seem to influence the occurrence and the seriousness of these accidents.