wire is placed in the vein. Studies are currently in progress to determine if a wire with a smaller radius of the J portion (1.5 mm) is able to improve the success rate.

Nevertheless, because cannulation of the external jugular vein is performed under direct vision, the risk of arterial puncture and pneumothorax is extremely low. If the J-wire will not pass into the thorax, an internal jugular venipuncture can be done without redraping. Physicians who are uncomfortable with insertion of a catheter in a central vein in children via the internal jugular or subclavian route, may feel more comfortable with this technique.

REFERENCES


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An Unusual Adverse Drug Reaction to Thiopental

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Despite extensive use of thiopental, fewer than sixty cases of adverse reaction, usually of an anaphylactoid type, have been reported during the past 25 years.1 Barbiturates can cause reactions other than an anaphylactoid type. One such reaction, fixed-drug eruption, is a distinctive eruption occurring as erythematous, well-demarcated plaques on skin and/or superficial erosions of the mucous membranes, which appear at the exact same site following each exposure to the offending drug.2 Crohn first described this reaction in himself in 1927, when he suffered a recurrent eruption associated with the use of barbituric acid in allonal.3 Since that time, barbiturates have been among the drugs most commonly implicated in this type of reaction.4

In a recent review of adverse effects of intravenously administered drugs,5 fixed-drug eruption was not mentioned, perhaps because this reaction is rare with thiopental, or the reaction is not readily recognized by anesthesiologists since it develops several hours after the conclusion of anesthesia. Although not as potentially serious as anaphylactoid reactions, fixed-drug eruptions can cause considerable discomfort which can be avoided by recognition of the disorder and exclusion of the offending drug. We, therefore, describe a patient who developed a fixed-drug eruption to thiopental on two consecutive occasions—the second of which could have been prevented by the recognition of the nature of the reaction on the first occasion.

REPORT OF A CASE

A 65-year-old man with a bladder tumor, underwent anesthesia for cystoscopy and bladder biopsy. He was premedicated with atropine and codeine and received thiopental iv, O2, N2O, and enflurane via an endotracheal tube. Following anesthesia, the patient complained of painful erosions of his lips which cleared without treatment over a period of days. Two previous anesthetics in which thiopental, fentanyl, and enflurane were given were uneventful (table 1).

Two months later, he again underwent cystoscopy and bladder tumor checkout. The anesthesia consisted of thiopental iv, O2, N2O and enflurane via a mask with no premedication. The procedure lasted 40 min. Eight hours later, the patient noted some swelling of his lips; and on the following morning noted several burning skin lesions on his hands, arms, and legs, as well as painful mouth lesions. This was accompanied by malaise but no fever.

He was referred to the Dermatology Clinic for evaluation of his lesions. On physical examination, he appeared in moderate distress from his skin and mouth lesions. His vital signs were normal and he was afebrile. His mouth and lips were markedly erythematous and eroded. There were several small vesicles present on his lips (fig. 1). Several well-demarcated violaceous, edematous and vesicular lesions were present on his hands, forearms, and legs (fig. 2). They ranged from 0.5 to 2.0 cm in diameter.

Laboratory data included a normal CBC, sedimentation rate, chemistry screen, and uric acid as well as negative KOH preparation of skin and mouth lesions. Cultures of both skin and mouth lesions were neg-
Table 1. Relationship of drugs used to the fixed-drug eruption

<table>
<thead>
<tr>
<th>Date of Aesthesia</th>
<th>Drugs Used during Anesthesia</th>
<th>Eruption Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-80</td>
<td>Thiopental, fentanyl, N₂O, O₂</td>
<td>—</td>
</tr>
<tr>
<td>6-80</td>
<td>Local anesthesia</td>
<td>—</td>
</tr>
<tr>
<td>10-80</td>
<td>Thiopental, enflurane, N₂O, O₂</td>
<td>—</td>
</tr>
<tr>
<td>3-81</td>
<td>Thiopental, enflurane, N₂O, O₂</td>
<td>+</td>
</tr>
<tr>
<td>5-81</td>
<td>Thiopental, enflurane, N₂O, O₂</td>
<td>++</td>
</tr>
<tr>
<td>9-81</td>
<td>Diazepam, enflurane, fentanyl, N₂O, O₂</td>
<td>—</td>
</tr>
<tr>
<td>12-81</td>
<td>Ketamine, enflurane, N₂O, O₂</td>
<td>—</td>
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</tbody>
</table>

Biopsy of a lesion on the hand was diagnostic of fixed-drug eruption. The epidermis showed many dyskeratotic keratinocytes with vascular degeneration along the basal layer. There was subepidermal separation of the epidermis from the dermis. The dermis exhibited a superficial and deep perivascular and interstitial dense infiltrate of lymphocytes, histiocytes, neutrophils, and eosinophils. Direct immunofluorescence of the skin lesion was negative.

Initial therapy included 60 mg prednisone per day, topical steroids to skin lesions, and topically administered lidocaine to the mouth lesions. Within one week, the lesions had improved dramatically and the patient was symptom-free.

Subsequent workup included negative patch testing to materials in the ventilatory mask and cleansing agent used in the patient's procedure, as well as screening chemicals of the North American Contact Dermatitis Group. All of the patient's medications other than the anesthetic agents were restarted at intervals, and there was no recurrence of the lesions.

A test for in vitro leukocyte histamine release in response to thiopental was performed. Venous blood was drawn from the patient and leukocytes isolated using the method of Thueson et al.² Aliquots (450 µl) of leukocyte suspension (10 × 10⁶ cells/ml) were incubated at 37°C for 45 min with 50 µl of thiopental solution in a range of concentrations (10⁻⁴ to 10⁻² mg/ml). Blanks with 50 µl of buffer in place of thiopental were included, and total leukocyte histamine was determined by boiling an aliquot of cells and buffer for 5 min. The reaction was terminated by centrifuging at 800 g for 8 min at 4°C. Histamine was determined, using the radioenzymase assay of Shaff and Beaven.³ Thiopental failed to cause histamine release from the patient's leukocytes in vitro in the range of concentrations used.

Three months later, the patient underwent a 4.5-hour cystectomy anesthesia, which consisted of all the drugs used in the previous procedures (table 1), with the exception of thiopental. Diazepam and cimetidine were used as premedication and induction of anesthesia was accomplished with iv diazepam. The anesthesia was uneventful and no similar eruption occurred.

Six months later, the patient underwent emergency surgery for the reduction of a large bowel volvulus. He was given no premedication. His anesthesia consisted of ketamine iv, etrane, N₂O, and O₂ via an endotracheal tube with no resultant eruption.

Challenge with thiopental was considered, but ruled out on the grounds that the exclusion test was very highly suggestive and challenge could have resulted in a more severe eruption with a painful mouth and skin lesion causing the patient considerable discomfort. Moreover, thiopental could readily be replaced as an anesthetic agent in future procedures.

Discussion

The eruption experienced by this patient was consistent both clinically and histologically with a fixed-drug eruption. Thiopental appears to be the causative agent since exclusion of this drug alone resulted in no eruption. The inclusion of cimetidine in the premedication is unlikely to have masked any reaction, as histamine does not play a role in this eruption. The fact that the patient had received thiopental on two previous occasions without complications is in keeping with the view held that this reaction is allergic in nature rather than idiosyncratic. Once established, this reaction tends to recur on subsequent exposures to the drug.²

Fixed-drug eruption is characterized by a reaction which occurs at the same site, following each drug exposure. It may occur on any part of the body but does have a predilection for hands, genitalia, and mucous membranes. It develops rapidly over 12 to 24 hours and most commonly consists of a well-demarcated flat oval or circular skin lesion measuring anywhere from a few millimeters to several centimeters in diameter. The lesion is initially erythematous, turning later to a dusky red or violaceous color. Occasionally, multiple lesions may occur and rather than being macular, they can be urticarial, nodular, or vesicular. Pruritus usually is absent but the lesions may cause pain or burning. Mucous membrane lesions may be superficial erosions and may simulate a herpes infection.
Fig. 2. (Left). Well-circumscribed disciform inflammatory lesion involving the web-space of the left hand. (Right). Well-circumscribed vesicular lesion over the distal phalanx of a finger.

If the offending agent is removed, the eruption diminishes over a period of days but often leaves some residual pigmentation. Subsequent attacks may be more severe but are not associated with anaphylactic reactions or the severe bullous eruption of Stevens-Johnson syndrome.

The combination of clinical data and distinctive histologic changes should allow the diagnosis to be made readily. Challenge with the offending agent will reproduce the lesions but may cause a more severe eruption and discomfort, particularly if mucous membranes are involved. Exclusion of the suspected drug usually suffices to alleviate the problem. Cross reactions within a group of compounds can occur.

The exact pathophysiologic mechanisms of this eruption are unclear. Gimenez-Camarasa et al. demonstrated the presence of a serum factor in patients at the acme of their eruption which caused lymphocyte transformation in vitro, particularly in the presence of the offending drug. Wyatt et al. found that serum drawn 90–105 minutes after challenge caused an inflammatory reaction when injected into a quiescent site.

In vitro leukocyte histamine release was shown to be a reliable test in the investigation of anaphylactoid reactions to muscle relaxants, with predictive value in regard to future clinical use of related drugs by Assem. Hirshman et al. applied this test in their investigation of a case of anaphylactoid reaction to thiopental and demonstrated significant histamine release. The fact that thiopental did not cause histamine release from our patient’s leukocytes supports the clinical observation made over the years that exposure to a drug, which has caused a fixed-drug eruption in a particular patient, is not associated with a risk of anaphylaxis.

Although not associated with potentially fatal sequelae, a fixed-drug eruption should be recognized since further patient discomfort can be prevented by exclusion of the offending drug from future therapy.

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REFERENCES