activity occurs; this would not be possible with extra-amniotic or oral administration. It should be emphasised, however, that hypertonic uterine activity did not occur in any patient in the present series.

Nearly 24% of patients receiving 2 mg PGE₂ compared with 48.5% receiving 5 mg PGE₂ went into "spontaneous" labour as a result of the treatment alone, while 28.4% and 12.1% respectively showed little significant improvement in cervical score. The last group is especially important. The results suggest that the second prostaglandin treatment was of possible benefit to patients who had failed to respond to the first application, as it reduced the incidence of caesarean section and made amniotomy technically simpler. Numbers are small, however, so the findings may still be considered as inconclusive. Deviations in uterine response cannot be explained simply. In addition to the difficulty of precise cervical assessment there may be as yet unexplained variations in the rate of absorption of the prostaglandins from the vagina. The concentration of circulating steroid hormones may be important, for evidence has been presented that oestrogens can provoke an endogenous release of prostaglandins.⁶ Increased experience and a further adjustment in the dosage of prostaglandins or in the viscosity and volume of the gel vehicle might enhance the results. Larger doses should be used with caution, however, to ensure that overstimulation of the uterus does not occur.

Our results suggest that this method of cervical ripening produces no adverse effects on the fetus. Nevertheless, patients with suspected placental insufficiency should be monitored for the first few hours after treatment in case of possible fetal compromise.

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Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam

J E HEGARTY, J W DUNDEE

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Summary

The occurrence of thrombosis and phlebitis after intravenous injection of 10 mg diazepam, 4 mg lorazepam, or 1-2 mg flunitrazepam was studied on the second or third and the seventh to 10th days. A significantly higher incidence occurred with all drugs on days 7 to 10 than on days 2 and 3. Painless thrombosis occurred much more often with diazepam than with the other two benzodiazepines. Its incidence was greater in small hand or arm veins than in large antecubital vessels.

Lorazepam and flunitrazepam therefore have clear advantages over diazepam.

Introduction

Opinions vary about the incidence and severity of venous sequelae after the injection of benzodiazepines. The ever-increasing popularity of these drugs as parenteral sedatives warranted a detailed study of their effects. We report here the findings of a study in which patients were given roughly

equivalent sedative doses of undiluted preparations of diazepam, lorazepam, and flunitrazepam and then followed up for 10 days.

Method

Unselected patients were given either 10 mg diazepam, 4 mg lorazepam, or 1-2 mg flunitrazepam intravenously into the largest available vein for sedation or preanaesthetic medication. There was no selection as to which drug was given. No other drug was given through the same needle (size 21 or 23 swg). Once the drug had been injected the needle was withdrawn immediately and a sterile swab was strapped to the injection site. A vein was not included when there was evidence of extravenous leakage or haematoma, or if it was used subsequently for venepuncture, or if an intravenous infusion was erected in that arm.

Each patient was seen by one of us on the second or third day after injection and again at seven to 10 days. The site of injection was examined for the presence of tenderness on palpation of the vein or venous thrombosis. Positive findings were classified as phlebitis (tenderness without thrombosis), thrombosis (painless hardening), or thrombophlebitis (combination of the above.) Thrombosis and thrombophlebitis were graded as localised (less than one inch) or extended.^{1 2}

Results

At seven to 10 days there was a significantly higher incidence of venous sequelae among patients who had received diazepam than among those who had received lorazepam ($\chi^2=5.89$; $P<0.02$) or flunitrazepam ($\chi^2=14.71$; $P<0.0005$). The incidences of sequelae after lorazepam and flunitrazepam did not differ significantly (table 1). In each series more patients had some form of venous damage after 7-10 days than after two or three, the total incidence being significantly different at the two observations times ($\chi^2=4.48$; $P<0.05$).

Department of Anaesthetics, Queen's University of Belfast, Northern Ireland

J E HEGARTY, MB, FFARCS, senior tutor

J W DUNDEE, MD, FFARCS, professor of anaesthetics

Incidence of sequelae occurring two to three days and seven to 10 days after intravenous injection of three benzodiazepines. Results are numbers (and percentages) of patients

Drug	Dose (mg)	No of patients	2-3 days				7-10 days			
			Phlebitis	Thrombosis	Thrombo-phlebitis	Total venous sequelae	Phlebitis	Thrombosis	Thrombo-phlebitis	Total venous sequelae
Diazepam	10	44	3 (7)	5 (11)	2 (5)	10 (23)	0	17 (39)	0	17 (39)
Lorazepam	4	40	0	3 (8)	0	3 (8)	0	6 (15)	0	6 (15)
Flunitrazepam	1-2	43	0	0	0	0	0	2 (5)	0	2 (5)

Painless thrombosis was the only complication noted at 7-10 days, by which time it had often extended to the upper arm and even into the axilla. In a few patients in whom we were able to continue observations thrombosis was found to persist for several weeks. Although the incidence of thrombosis greater than one inch did not vary with the three drugs (it occurred in 10 of the 17 on diazepam, 4 of the 6 on lorazepam, and 1 of the 2 on flunitrazepam), very long thrombosed segments of vein were found more often after diazepam.

Using the 7-10 day data, we studied factors influencing the occurrence of venous sequelae. Sequelae occurred in 13% of large veins compared with 26% of small and moderate sized vessels. Although there was a lower incidence of total sequelae in antecubital veins (12%) this was not significantly less than the incidence in wrist and hand veins (24%). Nevertheless, injection into large antecubital veins was followed by a significantly ($P < 0.05$) lower incidence of thrombosis (6%) than when smaller hand or wrist vessels were used (23%). Sequelae were more common in the older patients (see figure).

Discussion

This study has shown that venous thrombosis is a not infrequent consequence of the intravenous injection of undiluted benzodiazepines. It has also shown that there is a considerable difference in the response to individual drugs.

On the basis of differences of age and time of observation it is easy to see how one worker could find a 47% incidence of thrombosis after 20 mg diazepam,³ while others found only a 29% incidence after doses of up to 25 mg diazepam.⁴ A follow-up of two to three days underestimates the incidence of thrombosis, and this may explain the low figure of 3.5% venous sequelae recorded by Langdon *et al*⁵ in over 1500 patients given an average dose of 20 mg diazepam with a short follow-up.

The interdrug differences reported here may be of clinical importance. Lorazepam and flunitrazepam showed clear advantages over diazepam in this respect in doses that were roughly equivalent as sedatives.

Incidence of venous thrombosis at seven to 10 days after intravenous injection of 10 mg diazepam, related to age of patients.

Lorazepam was supplied by Dr T V A Harry of John Wyeth and Brother Ltd, and flunitrazepam by Dr L Arenillas of Roche Products.

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SIDE EFFECTS OF DRUGS

Cheilostomatitis associated with propranolol treatment

We report a case of dryness and ulceration of the lip and inflammatory leucoplacal changes in buccal mucosae thought to have been caused by propranolol treatment. So far as we know, a strictly cheilo-oral reaction to a beta-blocking agent has not previously been reported.

Case report

In December 1975 a 65-year-old woman was admitted to the department of otorhinolaryngology with ulcerations of the lower lip and buccal mucosae. She complained of dryness and soreness of the mouth. There were fissures and crusts on the lower lip. The buccal mucosa showed multiple bilateral leucoplacal changes surrounded by partly ulcerated hyperaemic areas. The areas felt indurated and the ulcerations bled readily. Biopsy and histological examination showed general inflammation, hyperkeratosis, and parakeratosis. She had no dryness of eyes or skin rashes. Haematological and serological examinations gave normal results.

The symptoms first appeared in December 1970, two weeks after starting treatment with propranolol tablets 120 mg/day (Inderal) for coronary heart

disease and hypertension. She had no history of allergy, rashes, or local mouth disease. In subsequent years her oral symptoms gradually worsened, being interrupted by incomplete remissions and quickly followed by relapses.

We thought her condition might be due to an adverse effect of propranolol, and the drug was discontinued immediately. Treatment with alprenolol tablets 400 mg/day (Aptin) was begun. No local treatment was given. The symptoms gradually subsided over 12 weeks. She was then challenged with propranolol tablets 120 mg/day. After a week all the local symptoms returned, lasting until the drug was withdrawn three weeks later. Treatment with alprenolol again led to remission. She was observed for a year, during which time there was no relapse.

Comment

The adverse effects of practolol are well known. Similar adverse reactions to other beta-blocking agents have been reported.¹⁻⁴ We have not seen any reports of strictly cheilo-oral reactions to beta-blocking agents, and this case may illustrate an unrecognised variant of mucocutaneous adverse response. The close relation in time between signs of disease and drug use implies a causal connection.

Wadskov *et al* have reported three cases of psoriasis-like reactions to propranolol,⁵ and ocular reactions and skin rashes possibly caused by propranolol have been reported in a few cases.⁶ Despite its