

Anterograde amnesic effects of pethidine, hyoscine and diazepam in adults

J. W. DUNDEE

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

S. K. PANDIT

Institute of Postgraduate Medical Education and Research, Chandigarh, India

Summary

1. The intravenous administration of 5 and 10 mg of diazepam caused anterograde amnesia in 50 and 90% of adults, the peak effect occurring in 2–3 min and action persisting for 20–30 minutes.
2. Hyoscine (0.4 and 0.6 mg) caused amnesia in 35 and 50% of patients with peak effect not occurring until 50–80 min after injection and action persisting for at least 120 minutes.
3. With neither drug was there any relationship between the incidence of amnesia and the degree of drowsiness.
4. Amnesia was not observed after saline or after 50 mg pethidine.
5. On questioning 6 h after a short operation many patients had no memory of an object which they clearly recognized and described 1 h after surgery.

Introduction

The ability of premedicant drugs to suppress memory for events immediately before and for a few hours after surgery would be most useful. However, a study of over 2,600 adult patients receiving a variety of standard premedicants given intramuscularly before minor gynaecological procedures carried out under a standard anaesthetic showed only a 5% incidence of impairment of memory immediately preceding the operation. Of the drugs studied only hyoscine (0.4 mg), hyoscine-diazepam (10 mg) or opiate-diazepam showed any promise in this field (Pandit & Dundee, 1970). In an extension of these studies, in which the drugs were given intravenously 10–15 min before operation, Pandit, Dundee & Keilty (1971) showed the patients an object to remember before injection and again 1 h after apparent return of consciousness, their memory for these and other preoperative events being tested 6 and 24 h later. Retrograde amnesia did not occur with any commonly used premedicants and was only observed with a mixture of pethidine (100 mg), diazepam (10 mg) and hyoscine (0.4 mg), which was too depressant for routine clinical use. This may have been associated with minor degrees of hypoxia, although Crow & Kelman (1971) have shown that mild acute hypoxia does not affect short term memory in man despite the findings of Thompson (1957) and Thompson & Pryer (1956) that this occurred in animals. The opiates caused very little anterograde amnesia either in the pre- or postoperative period but diazepam and hyoscine appear to have specific amnesia producing properties. The effect of both of these is enhanced by the addition of a narcotic analgesic. However, this study suggested a very different time-effect relationship with a clinical adult dose of diazepam (5 and

10 mg) and hyoscine 0.4 and 0.6 mg) and this difference is investigated in more detail.

Methods

Subjects were 160 fit women, of reproductive years, scheduled for minor gynaecological operations lasting 5–10 minutes. They were visited about 2 h before operation, and after explaining the procedure and being told that they were to participate in a study of memory, the test drug was injected intravenously over 1 minute. They were then shown postcards of familiar objects 1, 2, 3, 4, 5, 7, 10, 20, 40 and 60 min later and on each occasion they were questioned for a few seconds to be certain that they recognized the picture. The order of showing cards was constant throughout. (The exception to this was a second group of twenty patients given 0.6 mg hyoscine to whom objects were shown at 40, 60, 80, 100 and 120 min.) Ten minutes after injection the degree of drowsiness was assessed as good, fair, slight or nil according to the scheme described by Dundee, Moore & Nicholl (1962).

Patients were anaesthetized with methohexitone-nitrous oxide-oxygen and were usually awake within 20 min of the end of the operation. One hour after recovery they were shown a further familiar object and they were asked to describe it so as to ensure recognition.

Each patient was visited 6 h after operation and asked if she remembered the pictures shown to her. At first she was asked to recollect the pictures, not necessarily in the order shown (recollection), and then to pick the ten out of a bundle of 20 cards (recognition). On each occasion the memory of the cards was recorded as clear, hazy or nil. In the final assessment of amnesia the number of patients who failed to remember a particular card was recorded and the incidence of amnesia calculated for each time period. Sometimes patients 'identified' a wrong picture, but the number of such mistakes was very small and was ignored.

A further group of twenty 'control' patients was shown the objects but they were given no drug and had no operation.

Drugs were given 'blindly' in random order and consisted of diazepam (5 mg and 10 mg), hyoscine (0.4 mg and 0.6 mg) (2 studies), pethidine (50 mg) and saline, each being given to twenty patients.

Results

There were no great differences in the pattern of amnesia found on 'recollection' and 'recognition' in the different series but since the latter is considered to be a more standard method of assessment (Hetherington, 1962) only data obtained from recognition of objects are presented. There was virtually no amnesia in the control series, with only three of the twenty patients failing to recognize one of the objects.

Four typical results are shown in Fig. 1. It was found that the incidence of amnesia was still high 60 min after hyoscine, and thus the second series of patients was studied as shown in this figure, since it would have been unwise to have asked patients to recognize more than the standard ten objects.

There was no real difference in the incidence of both preoperative and postoperative anterograde amnesia with pethidine (50 mg) and saline. However, both diazepam and hyoscine produced a notable degree of amnesia. The differences in

the incidence, onset and duration of action of this are shown clearly in Fig. 2, diazepam having a rapid onset and transient effect while hyoscine has a slow onset and prolonged effect.

A comparison of the incidence of amnesia, and that of drowsiness found 10 min after injection of the drugs shows no constant relationship between these two facets of drug action (Table 1). At this time pethidine had a noticeable soporific effect with no action on memory. While overall incidence of drowsiness with diazepam and hyoscine was similar, the memory loss produced by the former was more marked.

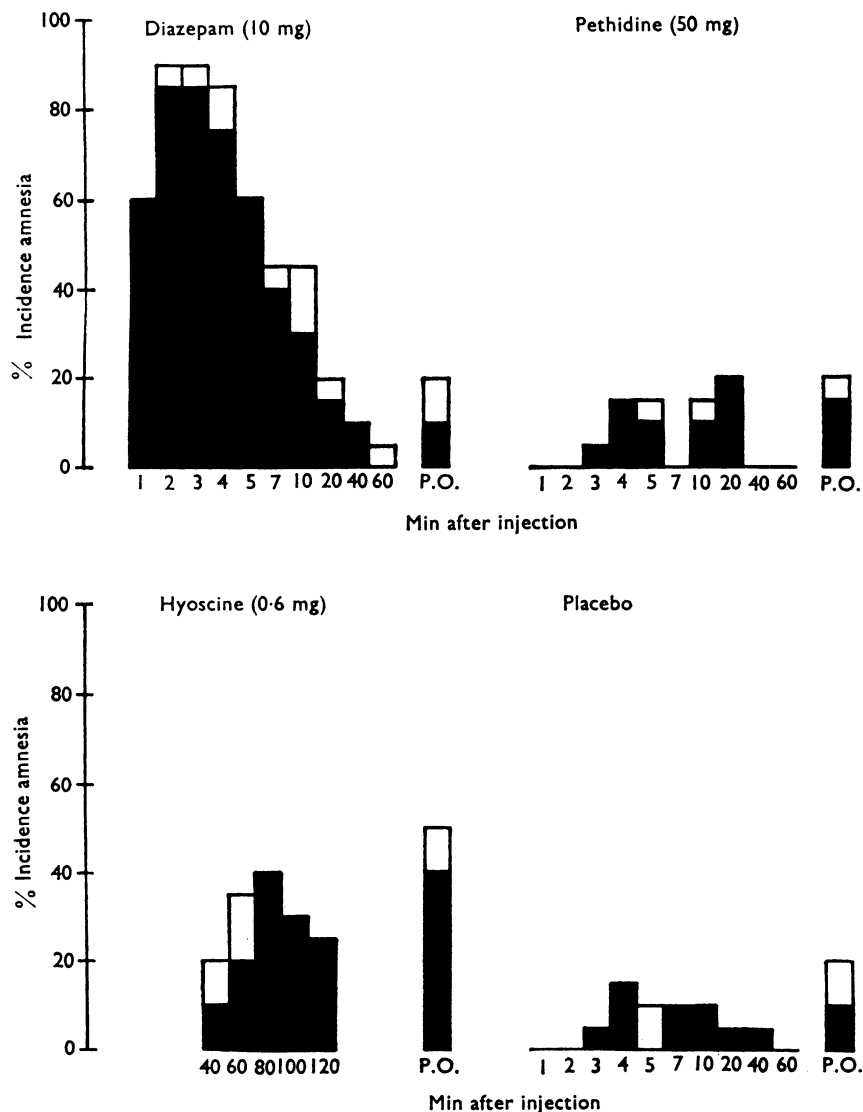


FIG. 1. Percentage incidence of complete ■ and partial □ anterograde amnesia observed after intravenous injection of four drugs with incidence of memory loss for an object shown 1 h after operation (P.O.).

Discussion

These findings substantiate the view that both diazepam and hyoscine have a specific amnesia producing action. In the usual adult clinical dose (10 mg) diazepam produces a profound effect with peak action occurring in 2-3 min and amnesia only lasting for 20-30 minutes. This is in keeping with the findings with its use before the administration of local anaesthesia for conservative dentistry when most patients have little memory of the intraoral injection (Keilty & Blackwood, 1969; O'Neil & Verrill, 1969; O'Neill, Verrill, Aellig & Laurence, 1970). In the light of the present findings it is not surprising that Pandit & Dundee (1970) found no anterograde amnesia for events occurring 60-90 min after its intramuscular injection.

Hyoscine is more widely known for its amnesic action, particularly in the field of obstetrics (Gauss, 1906) and its successful use in producing 'twilight sleep' is undoubtedly related to its prolonged action. This also explains the long period of postoperative amnesia following its premedicant use (Lambrechts & Parkhouse, 1961).

A not unimportant finding is the high incidence of apparently awake patients who have no clear memory of events occurring 1 h after a brief methohexitone-nitrous oxide anaesthesia. Even with no active premedication this was found in one-fifth of patients, the incidence being 50% when hyoscine was given.

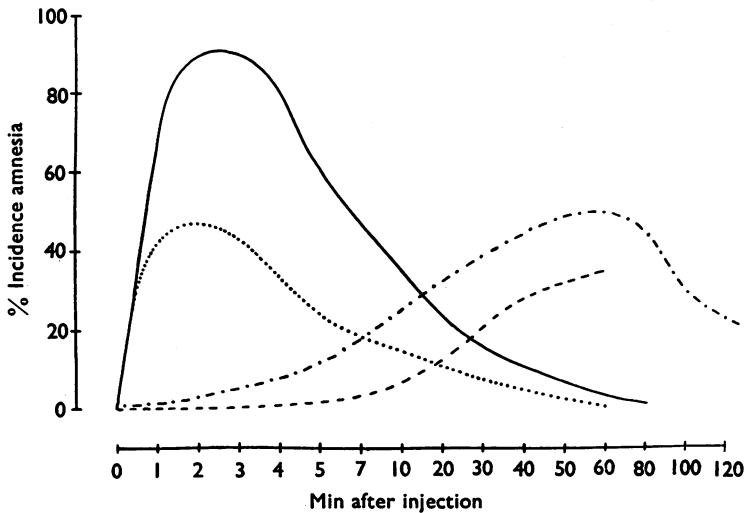


FIG. 2. Comparisons of the incidence of any degree of amnesia found after diazepam (10 mg) (—); diazepam (5 mg) (· · · ·); hyoscine (0.6 mg) (- · - · -); and hyoscine (0.4 mg) (- - - -).

TABLE 1. Percentage incidence of amnesia (recognition of objects) and drowsiness (notable=good plus fair) recorded 10 min after drug administration

Premedication	Amnesia		Drowsiness	
	Complete	Partial	Notable	Slight
Saline	10	0	0	25
Pethidine 50 mg	0	0	25	50
Diazepam 5 and 10 mg	33	7	66	13
Hyoscine 0.4 mg and 0.6 mg*	12	3	57	23

* First series only=objects shown during first hour after drug.

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