ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA
XI: TWO NON-PHENOTHIAZINE ANTI-EMETICS: CYCLIZINE AND TRIMETHOBENZAMIDE

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The use of anti-emetic drugs before, during and after anaesthesia has been the subject of much research and comment. Most publications deal specifically with the actions of these drugs in preventing and treating nausea and vomiting, although some attention has been paid to their side effects. While the largest number of anti-emetics in clinical use are phenothiazine derivatives, their toxicity should preclude their widespread application (Cullen, 1959). Because of this toxicity attention has focused on the non-phenothiazine anti-emetics and this paper deals with two of these: cyclizine and trimethobenzamide (fig. 1).

**FIG. 1**
Formulae of drugs studied.

Cyclizine hydrochloride, a member of the anti-histamine group of drugs, has been used in anaesthesia solely for its anti-emetic effects (Dent, Ramachandra and Stephen, 1955; Moore et al., 1956). These workers were enthusiastic about its ability to diminish pre-operative sickness, but more recently Bellville, Bross and Howland (1959) and Robbie (1959) have shown that it is less effective than the phenothiazines. No severe side effects have been reported from the use of cyclizine.

Studies in animals and humans have shown that trimethobenzamide is an almost specific anti-emetic (Schallek et al., 1959; Brandman, 1960). There are few reports on its efficacy in anaesthesia but in the treatment of nausea and vomiting due to other causes it has been found to be of definite value (Kolodny, 1960; Nathan, 1960).

**METHOD OF ANALGESIMETRY**

The effect of the drugs on the response to somatic pain was measured by the method described by Dundee and Moore (1960). When the intravenous route was employed the drugs were given over a period of 1 minute to healthy males scheduled for herniorrhaphy and readings were carried out at 5-minute intervals for half an hour. The effects are expressed as changes from the pre-injection readings. The drugs were also given intramuscularly with atropine 0.6 mg as premedication to healthy females prior to the operation of dilatation and curettage. The "double blind" technique was used so that the observer did not know the identity of the drug under investigation. The alterations in pain threshold and response readings were assessed between 60 and 90 minutes after injection in these patients and are expressed as the "analgesia index" (Moore and Dundee, 1961a; Dundee, Nicholl and Moore, 1961).

The doses employed were those most widely recommended for their anti-emetic activity, viz. 50 mg cyclizine and 200 mg trimethobenzamide.

**RESULTS**

The average effect of the intravenous injection of cyclizine 50 mg and trimethobenzamide 200 mg...
on the mean of the threshold and response readings in six subjects is shown in figure 2. This demonstrates that both drugs are capable of increasing sensitivity to somatic pain but the anti-analgesic action of cyclizine is more marked and more prolonged than that of trimethobenzamide.

The writers’ experience suggests that the rapid intravenous injection of these drugs had a negligible effect on cardiovascular haemodynamics, as compared with that of the phenothiazine derivatives. Cyclizine had a moderate sedative action and on two occasions caused marked restlessness, but neither of these effects occurred after the administration of trimethobenzamide.

The difference in the action of the two drugs on response to somatic pain is more evident when their analgesia indices are considered (table I). The anti-analgesic action of trimethobenzamide is obviously so transient as to have worn off within 1 hour of intramuscular injection and it has no appreciable effect on pethidine analgesia. Cyclizine, on the other hand, markedly increases sensitivity to pain and this action persists for at least 1 hour after intramuscular injection. Unfortunately, pethidine and cyclizine are not compatible in solution and it was not possible to investigate their action when administered together, because of the “blind” technique used in these studies.

**DISCUSSION**

This investigation demonstrates the ability of cyclizine in clinically used doses to increase sensitivity to somatic pain. It may be of clinical importance in the combination of analgesics with cyclizine which is popular in the management of chronic pain. Hougs and Skouby (1957) have noted that cyclizine has no analgesic activity but do not mention its anti-analgesic effect.

In previous studies it was noted that premedication with drugs having anti-analgesic activity increased the incidence of tremors and spontaneous involuntary muscle movement which followed the administration of a fixed dose of methohexitone (Moore and Dundee, 1961b; Dundee and Moore, 1961a, b; Dundee, Riding, Barron and Nicholl, 1961). In unpublished work it has been found that when using trimethobenzamide and cyclizine the incidence was as follows.

- Cyclizine 50 mg . . . 60%
- Trimethobenzamide 200 mg . 28%
- Atropine 0.6 mg . . . 29%
- Pethidine 100 mg.
- Trimethobenzamide 200 mg 13%
- Pethidine 100 mg . . . 6%

These are in keeping with previous observations and it is obvious that cyclizine cannot be recommended for use before methohexitone anaesthesia. Trimethobenzamide appears to be free from any such undesirable effects and if its antiemetic action is confirmed after more extended trials it should be a drug of some promise.

**SUMMARY**

Analgesimetry studies were carried out on healthy subjects following the administration of two non-phenothiazine anti-emetics, cyclizine and trimethobenzamide. An increase in sensitivity to soma-
tic pain followed the intravenous injection of clinically used doses of both drugs but this action was more marked and prolonged with cyclizine. Following intramuscular injection an anti-analgesic effect was present 60 to 90 minutes after cyclizine, but not after trimethobenzamide. The latter had no effect on pethidine analgesia.

The anti-analgesic action of cyclizine is associated with a very high incidence of excitatory phenomena following methohexitone and it is not recommended for use in pre-anaesthetic medication before methohexitone induction of anaesthesia.

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REFERENCES


SOMMAIRE

Des études d'analgésimétrie furent effectuées sur des sujets sains après l'administration de deux antivomitoires non dérivés de la phénothiazine: la cyclizine et le triméthobenzamide. Une augmentation de la sensibilité à la douleur somatique fut notée à la suite de l'injection intra-veineuse de doses cliniques des deux médicaments, mais cet effet fut plus marqué et plus prolongé avec la cyclizine. Après l'injection intraveineuse, un effet anti-analgésique fut enregistré 60-90 minutes après la cyclizine, mais pas après le triméthobenzamide. Ce dernier n'eut pas d'effet sur l'analgésie obtenue à la pethidine.

L'action anti-analgésique de la cyclizine est associée à une très haute incidence de phénomènes excitateurs après l'administration de méthohexitone, et son emploi en pré-anesthésie n'est pas recommandé avant l'induction de l'anesthésie par le méthohexitone.

ZUSAMMENFASSUNG
