TRIFLUPROMAZINE (VESPRIN®[1]) IN ANAESTHESIA: A CLINICAL EVALUATION

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DURING THE PAST DECADE many new sedative drugs have been introduced into clinical medicine with great success. The concept of tranquillizing action apart from any effects of hypnosis or analgesia has emerged. The term "ataraxia" meaning "calmness untroubled by mental or emotional excitement" was introduced by Fabing (1). Many well established drugs such as ethyl alcohol, the narcotics, and the barbiturates may produce these effects in addition to their other well-known properties, but are of limited usefulness when only tranquillity is desirable.

TABLE I

DIVISION OF TRANQUILLIZERS
(After Schiele and Benson)

			Dose in mg		
	Generic name	Trade name	Oral	I M	I V.
Major					
Phenothiazines	Chlorpromazine	Thorazine	50–100	25	5–10
	Promazine	Sparine	100	50	10
	Mepzaine	Pacatal	100	50	25
	Prochlorperazine	Compazine	10	5	
	Perphenazine	Trilafon	10	5–10	5–10
	Triflupromazine	Vesprin	25–50	20	5
	Promethazine	Phenergan	100	50	
Reserpates	Reserpine	Serpasil	0 25		
	Rescinnamine	Moderil	0 25		
	Deserpidine	Harmonyl	0 25		
Minor					
Alkanediols	Meprobamate	Miltown Equanil	800		
	Phenaglycodol	Ultran	600		
Diphenylmethanes	Hydroxyzine	Atarax	50	25	
	Benactyzine	Suavitil	3–5		
	Azacyclonal	Frenquel	20–100		10

In psychotic states, behaviour-modifying drugs have proved invaluable. Because of the stress and strain of modern living, drugs with a predominantly tranquillizing effect have extensive clinical application. A simple classification of most commonly used tranquillizing drugs is shown in Table I.

[1]Vesprin® is the trade name of triflupromazine Squibb

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Drugs of this nature have many advantages and disadvantages. Extensive work has been done in evaluating these compounds under various circumstances and continuing the search for even more satisfactory compounds. Because of their psychic modifying quality and their effects on the autonomic nervous system and the reticulo-activating systems, drugs of this type are of great interest and value to anaesthesiologists In an excellent review of the efficacy of ataractic drugs in clinical anaesthesia, Dobkin (3) emphasizes the need for evaluating new members of this group of drugs so that knowledge of the efficacy of each agent, coupled with a precise knowledge of its multiple actions and main dangers, may be used in a rational manner to the advantage of the patient and anaesthesiologist.

The phenothiazine derivatives deserve special consideration as drugs of this group, such as chlorpromazine, promethazine, mepazine and promazine, already have an established place in medicine. The phenothiazine compounds have a multiplicity of actions and produce many effects, some desirable and others undesirable, depending on the circumstances of administration.

In a search for more effective and less toxic phenothiazine derivatives with greater specificity of action, Vesprin® was developed by Yale at the Squibb Institute for Medical Research Vesprin has been given the generic name, triflupromazine, and chemically is 10-(3-dimethylaminopropyl)-2-(trifluoromethyl) phenothiazine hydrochloride Its structural formula and that of related compounds is shown in Figure 1.

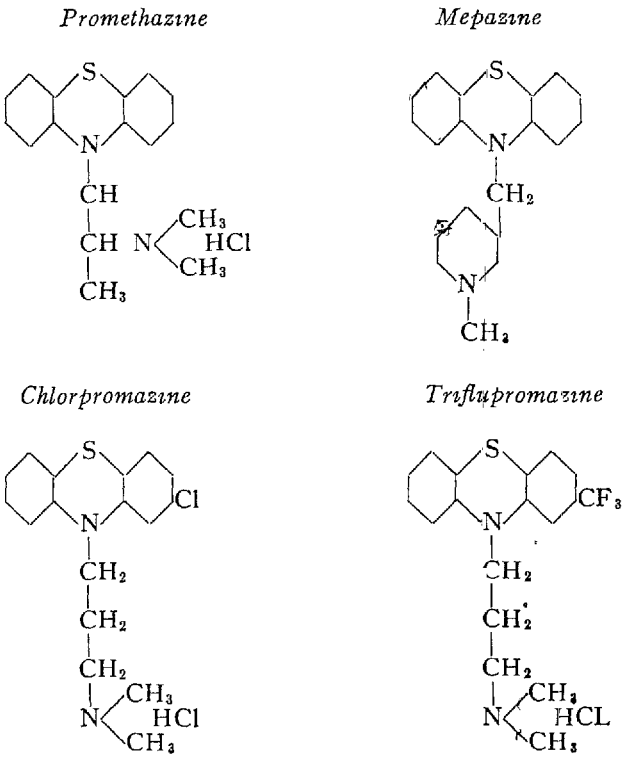

FIGURE 1 Structural formulae of some phenothiazine derivatives

Pharmacology

Animal

Pharmacological studies in various laboratory animals have shown that triflupromazine has sedative and depressant effects similar to those of chlorpromazine (in equal doses) but was three to five times as active as a tranquillizing agent and two to three times as potent in inhibiting conditioned response. The anti-emetic activity of triflupromazine in dogs was from five to ten times greater than that of chlorpromazine. Triflupromazine produced minimal analgesic effects, but potentiated the analgesic effect of morphine

Antagonism to amphetamine and lysergic acid diethylamide has been demonstrated but no anti-nicotinic effects Renal haemodynamics were not affected.

Effects on the autonomic nervous system were similar to those of chlorpromazine but were fewer and less pronounced in that tachycardia was not prolonged following doses of triflupromazine in clinical range and hypotension was less sustained. The carotid pressor response was blocked and postural hypotension could occur.

Triflupromazine had a slight anti-parasympathetic activity.

As acute toxicity was similar for the two drugs, triflupromazine appeared to be relatively more potent than chlorpromazine as a tranquillizing agent, so possessing a greater margin of safety (4–9).

Human

Although accurate inference cannot always be made from the results of experiments with animals, studies on human patients have produced similar results Adverse effects on hepatic function or on the blood picture were not detected, even after prolonged administration Hypotensive effects were not troublesome except when doses, now considered excessive, had been given intravenously.

Clinical Reports

Triflupromazine has been used extensively by many investigators, mainly in psychotic patients, and has been found effective in modifying aggressive and hostile behaviour, in alleviating delusions and hallucinations and for controlling agitation, anxiety, and panic. Behaviour is modified with a minimum of side-effects (10–15). The potent anti-nauseant effect has been confirmed by Stone (16), Westphal (17), and by Adriani (18).

Triflupromazine has been given in pre-anaesthetic medication to 1,400 children prior to general anaesthesia, and before local anaesthesia to 780 patients by Stone (19), as adjunctive medication to block anaesthesia by Wentzler (20); as an adjunct to obstetrical analgesia during labor by Weber (21); and in control of postoperative nausea and vomiting by Bowman (22). Results, at least satisfactory, have been reported by all of these authors.

Supply

Triflupromazine (Vesprin®) is at present available as tablets containing 10, 25, and 50 mg. of base (as hydrochloride); as a palatable suspension 10 mg./cc, and in aqueous solution in 1 cc. ampoules, or 1 cc. rubber-capped vials containing 20 mg./cc. The pH of this solution is 4 1. At pH 6.4 the compound precipitates from solution. Solutions of triflupromazine are not physically compatible with barbiturate solutions such as thiopentone or pentobarbital, but can be mixed with meperidine, other phenothiazine compounds, and all commonly used intravenous fluids

Present Clinical Study

As an adjunct in anaesthesiology we have administered triflupromazine to 1,577 patients (Table II)

TABLE II

Anaesthesia	I M	I V	Total
Local	638	17	655
General	702	23	725
Spinal	128	39	167
Postoperatively		30	30
Total	1,468	109	1,577

Local Effects

Although all phenothiazine compounds can be irritating to tissues, no local reaction has been noticed nor have complaints of prolonged soreness followed intramuscular injection. After intravenous administration, even when undiluted, no phlebothrombosis has been observed and no complaints of pain following injection have been noted.

Dosage

Triflupromazine was given as pre-anaesthetic medication alone or in combination with meperidine, pentobarbital, atropine, or scopolamine to a series of 1,468 patients An additional 79 patients received triflupromazine intravenously during anaesthesia, and 30 patients intravenous triflupromazine post-operatively after general anaesthesia.

The preoperative evaluation of the patients revealed many abnormal conditions including cardiovascular, pulmonary, metabolic, hepatic, renal and neurological complications. The observations made with each of the three groups of patients follow.

General Anaesthesia

There were 725 patients ranging in age from 3½ months to 87 years, 368 being children under 14 years. Weight ranged from 15½ to 247 lb. The patients were about equally divided as to sex.

The usual *intramuscular* dose of triflupromazine Vesprin®) in adults was 20 mg., but elderly or debilitated persons were given half this amount. Early in the series children were given 1 mg per year of age but later, as children need

relatively more sedation than adults and tolerate triflupromazine well, children under 5 years of age were given 5 mg., those 5 to 10 years old 10 mg., and those older than 10 were given the adult dose. The *intravenous* dose was originally one-half the intramuscular dose, but when it was realized that almost maximum benefit with far less undesired effects could be obtained by even smaller doses, it was changed to the present dose of 5 to 7½ mg. for adults, 2–3 mg. for children age 7 to 14; and 1–2 mg. for children under 7 years of age. This concept is being further investigated (see discussion). The most effective tranquillization appears 45 to 60 minutes after an intramuscular dose or 3 to 5 minutes after an intravenous dose.

All common operative procedures were represented in the series, including 20 intracranial, 19 intrathoracic, and 10 intracardiac operations. There was no selection of patients and many of the patients were considered "poor risks."

When triflupromazine was given alone, patients became calm but not drowsy or euphoric Little analgesia was noted. When meperidine (dosage 50–75 mg for adults, 0.5 mg./lb. to children) was given as well as triflupromazine sedation was better, in that patients were tranquil and drowsy but readily roused. Patients were co-operative, but without excitement, especially of the barbiturate type. A few were asleep when left undisturbed but awoke readily. Most rested peacefully and although alert mentally appeared to be unusually calm in the acceptance of their surroundings. Combination therapy was particularly beneficial in apprehensive children, in whom it is often difficult to attain sedation without depression These children would tolerate venipuncture with unusual equanimity.

Sedation was considered unsatisfactory in 31 patients (4 4 per cent). Most of these were children who had received triflupromazine alone according to the original smaller dose schedule. Excitement was rarely seen, even with open-drop ether anaesthesia induction. No respiratory or cardiovascular depression was seen, even in elderly patients. An occasional mild tachycardia was noted in a few patients, but this reverted to a normal rate after general anaesthesia was induced.

Salivary secretions were generally reduced when triflupromazine was given alone although the mouth was not completely dry Usual or reduced doses of atropine or scopolamine, in addition, were effective in controlling secretions during subsequent anaesthesia.

Potentiation of meperidine was apparent Barbiturates such as pentobarbital and thiopentone were potentiated to a lesser extent and although subsequent anaesthesia tended to be smoother than usual it was felt that anaesthetic agents such as ether, cyclopropane, nitrous oxide, or Fluothane were not potentiated.

Postoperative reflexes returned as usual, but less analgesics were required for control of pain for six to eight hours postoperatively.

A complete record of postoperative nausea and vomiting was not kept for these patients, but it was felt that the incidence was reduced, particularly in children following operation for removal of tonsils and adenoids.

In the recovery room triflupromazine was administered intravenously to 17 adults and 13 children suffering from nausea and vomiting following general anaesthesia. All of the children and 15 of the adults were completely relieved.

Good sedation was also obtained and no hypotension or states of semi-consciousness were seen when the smaller intravenous doses were not exceeded.

Trifluprornazine greatly facilitated cooling in three patients when a hypothermic technique was employed.

Local Anaesthesia

There were 638 patients (ages 17 to 87 years) undergoing ophthalmic surgery. Of these, 469 were operated on for cataract extraction. Trifluprornazine (20 mg.) was usually given intramuscularly at bedtime the previous night; 487 of the 507 patients so treated slept well during the night before surgery. One hour before surgery, 20 mg. of trifluprornazine were given with meperidine (35 to 100 mg.) and in younger or apprehensive patients pentobarbital (25 to 100 mg).

It was found that the effect of combinations of these drugs gave better sedation than when used alone. Sedation was usually excellent. A typical patient was relaxed and drowsy, neither excited nor euphoric, co-operative during the surgical procedure, obeying and remembering instructions. The analgesia produced by meperidine provided relief from the slight pain and discomfort of the initial injection of the modified Von Lint infiltration.

There was no respiratory depression, but in view of possible hypotension, blood pressure was carefully recorded in 150 patients before medication was given and compared with pressures found after premedication and followed for six hours postoperatively and the next day.

A drop of 25 per cent or more was found in 29 patients (19 3 per cent) Of these 14 occurred before, 13 during, and 2 after surgery.

Initially great concern was felt as possible deleterious effects from the hypotension were anticipated However, as no ill effects had been observed during a comparable group of patients receiving similar premedication previously, it was assumed that the vital organs were protected by vasodilation maintaining normal blood flow, in spite of the hypotension This hypothesis was suggested by Buxton-Hopkins (23) and by Lear (24) during work on chlorprornazine. No active therapy was instituted, the pressure returning to normal limits in four to six hours.

Hypotension in other patients (not in this particular series) responded to vasopressors such as methoxamine and desoxyephedrine in doses of 2–5 mg. intravenously and/or 5–15 mg. intramuscularly. The response was more prompt and sustained with desoxyephedrine than with methoxamine, suggesting that trifluprornazine may have some indirect cardiac effect in addition to the vasodilatation.

It was thought that the combination with meperidine was mainly responsible for producing hypotension. A series of patients in a similar age group undergoing transurethral prostatic surgery was premedicated with meperidine alone or with trifluprornazine only. The incidence of fall of blood pressure of over 25 per cent of initial values was 8.3 per cent with trifluprornazine and 18.5 per cent with meperidine.

Subsequently, reducing the dose of meperidine in elderly or hypertensive

patients greatly reduced the incidence and severity of hypotension in this series.

Of the patients undergoing cataract surgery, 4 05 per cent were nauseated and vomited during the postoperative perioc after receiving trifluprornazine, compared with 13.7 per cent of those receiving the meperidine-pentobarbital combination with no trifluprornazine, and 10 0 per cent of those receiving the usual premedication but with promethazine added.

This reduced incidence of nausea and vomiting was found to be statistically highly significant ($\chi^2 = 19.75$, $p = < 001$).

So pleased and enthusiastic were the ophthalmic surgeons about the usefulness of trifluprornazine in premedication that this series is being made the basis of a separate and detailed report

Seventeen patients received intravenous trifluprornazine for supplementary sedation during various general surgical operations under local anaesthesia. Sedation was good in all cases and it was found that adequate sedation with minimal hypotensive effects could be obtained with doses of 5 mg. with an additional one or two doses of 2 5 mg if necessary. The only falls of blood pressure greater than 25 per cent were seen early in the series when excessive doses of 20 mg. had been given intravenously

Spinal Anaesthesia (181 patients)

An intravenous injection 5–10 mg trifluprornazine produced a marked sedative and quieting effect with no change in blood pressure or pulse rate in 39 patients who became apprehensive during surgery under spinal anaesthesia.

Trifluprornazine (20 mg intramuscularly) was given 1 hour before surgery to 142 patients, 120 of these receiving this drug alone Sedation was good but not so striking as in apprehensive children. Hypotension, particularly postural, was watched for as the patients sat for lumbar puncture A drop of over 29 mm. Hg occurred in 21 patients, with a drop greater than 25 per cent of initial value in 10 (8.3 per cent), while 5 patients fainted on sitting, 4 with hypotension. All patients who fainted had been sitting upright for 12 minutes

No exaggerated hypotension followed the onset of spinal anaesthesia and vasopressors in usual dosage when used prophylactically or therapeutically produced the expected response.

Possible Complications

Untoward effects Three patients developed skin rashes postoperatively. Two were considered to be penicillin reactions and one an urticarial type of blood transfusion reaction None of these reactions was considered the result of trifluprornazine

Two patients, ages 85 and 79 respectively, developed cerebral thrombosis after cataract surgery. As both patients were known to be suffering from arteriosclerotic hypertensive cardiovascular disease, and hypotension was not present following the administration of trifluprornazine, this drug was not considered contributory.

Agranulocytosis or extrapyramidal hyperactivity were not seen. No clinical evidence of renal or hepatic toxicity was noted in this series.

Discussion

Whatever one's opinion may be regarding the usefulness and indications for using ataractic drugs in anaesthesiology, it must be agreed that new, powerful and interesting drugs have been added to the anaesthesiologists's armamentarium.

In this clinical study it was convenient to compare the effects of trifluprómazine with those of chlorpromazine or promazine which are the best-known phenothiazine derivatives.

It was found that less somnolence was produced but better psychic sedation and tranquillity, co-operation being particularly marked during venipuncture or operation under local anaesthesia. No tissue irritation was seen. A consistency of effects and predictability of action were noted for six to eight hours. The incidence of nausea and vomiting was significantly reduced when evaluated in ophthalmic surgery. The incidence of hypotension was not great or of severe degree and can probably be reduced to an insignificant level by reducing the amounts of narcotics administered simultaneously, and by using relatively small but effective doses of trifluprómazine.

The concept of "sub-toxic" doses is emerging. Is it possible to arrive at a particular dose of a specific drug that will give maximum beneficial effects with minimal undesired effects? In the case of phenothiazine compounds it is likely that this can be attained by selective synthesis. Chlorpromazine has a multiplicity of actions, some good, some bad, depending on the circumstances for which it is given. In the case of trifluprómazine it is hoped that one can arrive at a dosage schedule that will give very good tranquillization without appreciably lowering the level of consciousness; a profound anti-nauseant effect with little effect on the cardiovascular system. Under different circumstances one's opinion on which are desirable or undesirable effects would be different.

Investigation along these lines regarding both intramuscular and intravenous doses is continuing.

Conclusion

Trifluprómazine (Vesprin®), a phenothiazine derivative, appears to be a very useful drug in pre-anaesthetic medication.

It is a potent anti-nauseant; psychic sedation is good, and clouding of consciousness and hypotensive effects are minimal.

Summary

Tranquillizing drugs are of great interest to anaesthesiologists. The investigation of new compounds continues in the hope of finding even more satisfactory agents.

The pharmacology of trifluprómazine is briefly reviewed and also the clinical findings of other investigators.

This report deals with the clinical findings after giving trifluprómazine to 1,577 patients (postoperatively, 30; pre-anaesthetic—local 655, general 725, spinal 167).

Favourable effects including good psychic sedation without mental clouding; significant decrease in postoperative nausea and vomiting; moderate potentiation of narcotics; slight potentiation of barbiturates, minimal potentiation of anaesthetic agents; no respiratory depression or evidence of toxicity to the renal, hepatic or haemopoietic systems.

Better sedation is attained by combination with small amounts of meperidine and/or pentobarbital Side-effects are minimal if dosage of all agents is chosen with care. Such combinations are considered very satisfactory prior to local analgesia.

Though some hypotension was seen, its incidence and severity can be minimized by careful selection of dosage.

Further investigation of this agent is considered desirable

RÉSUMÉ

Les substances tranquillisantes sont d'un grand intérêt pour les anesthésiologues. La recherche de nouveaux produits se poursuit dans l'espoir de trouver des médicaments plus satisfaisants.

Nous avons étudié brièvement la pharmacologie de triflupromazine (Vesprin®) les résultats cliniques d'autres chercheurs.

Ce travail présente les résultats cliniques de l'usage de triflupromazine chez 1,577 malades (dont 30 cas après l'opération et, avant l'opération, 655 cas de locale, 725 de générale et 167 de rachidienne).

Nous avons observé, parmi les effets désirables, un calme psychique sans obnubilation mentale; une diminution appréciable des nausées et vomissements post-opératoires, une potentialisation légère des narcotiques, de même qu'une potentialisation légère des barbituriques et une potentialisation moindre des agents anesthésiques; aucune dépression respiratoire, aucune manifestation de toxicité sur le rein, le foie ou le système hémopoïtique.

On obtient une meilleure sédation si on l'associe au mepéridine ou au pentobarbital. Les effets indésirables sont réduits si l'on choisit le dosage avec soin. Avant l'anesthésie locale, ces mélanges donnent de bons résultats.

En déprit du fait que nous avons observé des cas d'hypotension, cette hypotension peut être raréfiée et moins sévère si l'on choisit bien le dosage.

Il s'impose de faire de plus amples recherches sur cette substance.

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