

From the Departments of Dermatology and Clinical Pharmacology,
Karolinska Sjukhuset and the Department of Pharmacology, Karolinska Institutet,
Stockholm, Sweden.

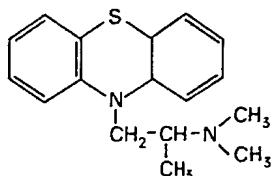
COMPARISON OF
THE ANTIHISTAMINIC EFFECTS IN SKIN OF
A TERTIARY (PROMETHAZINE) AND A
QUARTERNARY PHENOTHIAZINE
(N-HYDROXYETHYLPROMETHAZINE)

By

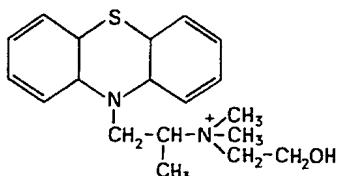
ÖSTEN HÄGERMARK & KJELL STRANDBERG

Most antihistaminic drugs have sedative effects, which to some extent limit their clinical use. Promethazine is a phenothiazine with strong antihistaminic and sedative actions. It is a tertiary ammonium compound passing readily through the "blood-brain barrier" into the central nervous system. When studying a series of quarternary derivatives of promethazine, Schmitterlöv and associates found that in animal experiments N-hydroxyethylpromethazine chloride (Aprobit®) (Fig. 1) had an antihistaminic activity comparable to that of promethazine, but that it did not enter the central nervous system and thus had no sedative effects (1, 4, 5).

However, the general clinical impression is that after peroral administration the antihistaminic potency of N-hydroxyethylpromethazine is low in comparison to that of promethazine. Experiments in the rat have indicated that N-hydroxyethylpromethazine is absorbed from the gastrointestinal tract to a lesser extent than promethazine (5). In view of this observation and the lack of data on the pharmacokinetics of N-hydroxyethylpromethazine in humans, we have compared the



PROMETHAZINE



N-HYDROXYETHYLPROMETHAZINE

Fig. 1.

antihistaminic effect of these two drugs given orally and parenterally in man. The area of the erythema (flare) and the duration of the itch response produced by histamine and the histamine liberator trypsin were used as test parameters.

MATERIAL AND METHODS

Twenty-one volunteer patients, aged 18–57 years and treated at the Dermatological Department for various dermatoses, took part in this investigation. The following conditions had to be fulfilled in the patients selected: they should feel itching after an injection of histamine; they should not be receiving treatment with antihistamines; and they should have no skin lesions on their upper arms. The solutions of histamine and trypsin (about 0.02 ml) were injected intracutaneously on the lateral aspects of the upper arms. The duration of the itch was determined and the size of the flare was measured 5 min after injection, as described earlier (6).

Antihistamine and placebo tablets were given according to a double-blind, cross-over scheme. The subjects received three doses, one at 3 p.m., one at 11 p.m., and one the following morning 3 h before the test. The second test was done 3 d later, after dosing according to the same time schedule as before. Promethazine (Lergigan®, Recip, Stockholm, Sweden) and N-hydroxyethylpromethazine (Aprobit®, Recip) were administered as 25 mg coated tablets. The placebo tablets contained lactose only and were coated similarly.

In the experiments where N-hydroxyethylpromethazine or promethazine were injected intracutaneously, histamine and the antihistamines were dissolved in saline, and the solutions were mixed to give the final concentrations stated.

RESULTS

Table 1 and Fig. 2 show the antihistaminic effects of promethazine and N-hydroxyethylpromethazine on oral administration as compared with placebo. N-hydroxyethylprometha-

TABLE 1

Effect of Promethazine and N-hydroxyethylpromethazine on the Itch and Flare Responses Elicited with Histamine and Trypsin.

Exp. series	Treatment	Histamine, 10 µg/ml		Trypsin, 100 µg/ml	
		Itch duration (sec)	Flare (mm ²)	Itch duration (sec)	Flare (mm ²)
I (n=11)	Placebo	67 ± 15	824 ± 81	63 ± 8	488 ± 85
	Promethazine, 25 mg × 3	7 ± 3**	206 ± 44***	30 ± 9***	156 ± 34***
II (n=11)	Placebo	84 ± 13	862 ± 139	83 ± 16	484 ± 80
	N-hydroxyethyl- promethazine, 50 mg × 3	83 ± 16	727 ± 111	84 ± 19	424 ± 83
III (n=10)	Placebo	100 ± 27	730 ± 90	74 ± 18	556 ± 85
	N-hydroxyethyl- promethazine, 100 mg × 3	63 ± 21	438 ± 67*	63 ± 16	356 ± 74*

Mean ± SEM

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

zine (50 mg t.i.d.) did not significantly decrease the responses elicited by either histamine or trypsin; a double dose (100 mg t.i.d.) reduced the itch duration and the flare caused by histamine by 37 per cent and 40 per cent respectively. The effects on the responses to trypsin were of a similar magnitude. In contrast, promethazine reduced the itch duration and the flare significantly even when given in a dose of 25 mg t.i.d. In Table 2 it is shown that N-hydroxyethylpromethazine produced no sedative effects in the doses used, whereas promethazine had a marked sedative action.

The antihistaminic effects of the two compounds on intracutaneous injection are shown in Table 3. Both compounds were mixed with histamine, and the mixtures were injected. It can be seen that the two compounds were about equipotent when administered by this route.

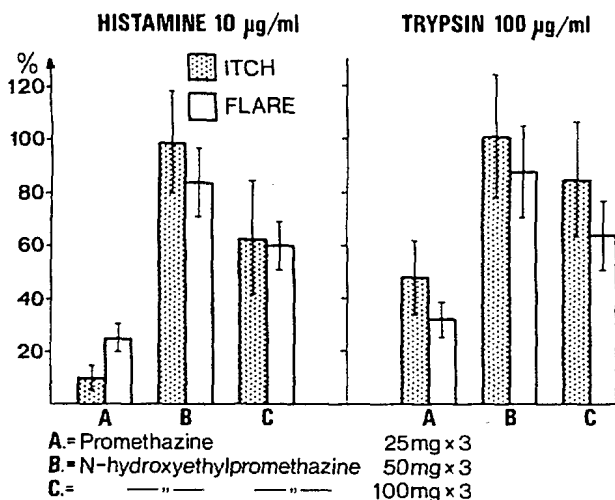


Fig. 2.

Effect of promethazine and N-hydroxyethylpromethazine on the itch and flare responses elicited with histamine and trypsin. Values expressed as percentage of responses obtained after placebo administration.

DISCUSSION

The highest peroral dosage (300 mg pro die) of N-hydroxyethylpromethazine used in this study exceeds that recommended by the manufacturer (200 mg). Yet with this dose the antihistaminic activity was weaker than that observed with the 4 times lower dose of promethazine. The sedative action of promethazine could not account for this difference as it is known that the antihistaminic and antipruritic effects of antihistamines in the present test system are not related to their sedative action (6). In contrast to the results obtained on peroral administration, the two compounds were equipotent on intracutaneous injection. Evidently, the reason for this is related to differences in the pharmacokinetics of the two compounds.

However, little seems to be known about the pharmaco-

TABLE 2

Sedative Effect of the Drugs. The Figures denote Number of Patients.

	o	+	++	+++
Placebo (n = 21)	18	3		
N-hydroxyethyl-				
promethazine, 50 mg $\times$ 3 (n = 13)	11	1	1	
„ 100 mg $\times$ 3 (n = 11)	10	1		
Promethazine, 25 mg $\times$ 3 (n = 11)	1	3	4	3

o = no sedation

+ = slightly tired

++ = tired or sleepy

+++ = very sleepy

TABLE 3

Effect of N-hydroxyethyl-promethazine and Promethazine Injected simultaneously with Histamine, 10 μ g/ml.

		Itch duration (sec)	Flare (mm ²)
Histamine only		197 $\pm$ 39	807 $\pm$ 99
„ + N-hydroxyethyl-			
promethazine,	0.1 μ g/ml	154 $\pm$ 32*	671 $\pm$ 102**
„ + „	1.0 μ g/ml	66 $\pm$ 16**	445 $\pm$ 102***
„ + „	10.0 μ g/ml	21 $\pm$ 9**	240 $\pm$ 61***
„ + promethazine,	0.1 μ g/ml	139 $\pm$ 28*	611 $\pm$ 105**
„ + „	1.0 μ g/ml	93 $\pm$ 19**	452 $\pm$ 90***
„ + „	10.0 μ g/ml	50 $\pm$ 17**	232 $\pm$ 56***

Mean $\pm$ SEM (n = 11)* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

kinetics of N-hydroxyethylpromethazine in man. It is known from animal experiments, that N-hydroxyethylpromethazine is absorbed to a lesser extent than promethazine from the gastrointestinal tract (5). This finding is in accordance with the view that high lipophilicity of a drug favours its absorption (3). The introduction of a quarternary nitrogen group in the

promethazine molecule results in a more hydrophilic compound with reduced capacity to pass through biological membranes as compared with the parent compound. By analogy, quarternary anticholinergic drugs show a low degree of absorption on oral administration (2, 7).

In addition, the polar nature of N-hydroxyethylpromethazine could be expected to favour a rapid excretion of the drug once absorbed, and thus the plasma/tissue gradient would tend to be low. However, experiments in rats with labelled compounds did not show a more rapid excretion of N-hydroxyethylpromethazine than of promethazine (5). Furthermore, the pharmacological half-life of N-hydroxyethylpromethazine was as long as that of promethazine when the two compounds were given intramuscularly to guinea-pigs (1). All these data indicate that differences in the degree of absorption might account for the differences in antihistaminic potency on oral administration observed in the present study.

SUMMARY

The antihistaminic effects of promethazine (Lergigan) and N-hydroxyethylpromethazine (Aprobit), a tertiary and a quarternary phenothiazine, respectively, were compared in man after oral and intracutaneous administration. The effects of the compounds were evaluated by studying their ability to diminish the flare and itch responses in human skin after intradermal injections of histamine and trypsin. On oral administration the quarternary compound had much less antihistaminic activity than the tertiary compound, whereas the two drugs were equipotent on intracutaneous injection. The difference in potency on oral administration is ascribed to a lower degree of absorption of N-hydroxyethylpromethazine than of promethazine.

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Author's address:

Östen Hägermark
 Department of Dermatology
 Karolinska Sjukhuset
 S-104 01 Stockholm 60
 Sweden

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