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A CLINICAL STUDY OF METHAQUALONE: A NEW NON-BARBITURATE HYPNOTIC

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THAT increasingly large numbers of people seek the aid and solace of central nervous system depressant drugs to enable them to cope with the trials and stresses of modern-day living must be accepted as an unpalatable fact. Physicians are faced with the problem of meeting this situation, and apparently do so by prescribing literally tons of barbiturates, other sedatives and tranquillizing drugs. Patients most frequently request "something to help me fall asleep", and for this purpose the mainstay has been the administration of one or other of the barbituric acid derivatives. These are certainly effective, but it is becoming quite apparent that they are not entirely innocuous. Habituation, accidental overdosage,[1] excitation rather than depression in the young and the very old,[2] and other less common serious untoward effects have led to legislation to restrict the freedom with which these drugs may be obtained. It is not surprising, therefore, that there should be intensive investigation directed to the re-evaluation of older preparations and of new drugs which may have less potentiality for harm. Chloral hydrate and paraldehyde are examples of older drugs which have been resurrected. These, however, present problems of taste and odour which make them unacceptable to most patients. Glutethimide and methylpyrolon are examples of non-barbituric acid derivatives which have recently been introduced.

The present study is concerned with an evaluation of a new non-barbiturate hypnotic, methaqualone (2-methyl-3-o-tolyl-4-quinazolone hydrochloride). Gujral *et al.*[3-6] called attention to the hypnotic properties of a series of quinazolone derivatives. The most promising of these was methaqualone, which has the following structural formula:

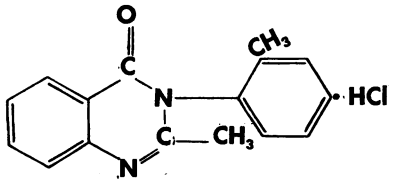

Fig. 1

Boissier, Dumont and Malen[7] carried out an extensive pharmacological investigation of this compound and concluded, in agreement with Gujral, Saxena and Tiwari,[4] that this compound possessed good hypnotic activity. It has low toxicity with a very favourable therapeutic index; 4 as compared with 2.5 for phenobarbital. Induction is rapid and sleep is not preceded by any stage of excitement or motor incoordination; recovery is smooth and calm. The drug strongly antagonizes the convulsive effects of pentylenetetrazol, but has little effect on the convulsive effects of strychnine or picrotoxin, indicating that its effects are on the cortex, with minor or no effect on the bulbar region or spinal cord. The drug definitely reduces the intensity of the action of central nervous system stimulants such as amphetamine, piperadol and caffeine. Methaqualone and the following drugs: chlorpromazine, pethidine, opiates, and dextromoramide, are mutually potentiating when administered together.

In chronic toxicity studies in rats and dogs, long-term feeding with doses of 40 to 50 mg. per kg. daily for five days per week for three to five weeks showed no evidence of toxicity. Growth, blood picture, and renal function were unimpaired. In a later study Boissier and Font du Picard[7a] demonstrated that methaqualone potentiates the analgesic action of codeine.

With this favourable pharmacological background, Ravina[8] undertook a clinical evaluation of methaqualone. One hundred patients were given the drug in a dose of 150 mg. orally or 200 mg. as a rectal suppository. Sleep occurred rapidly, usually within 10 to 20 minutes, and induction was not preceded by motor or psychic excitement. Sleep lasted for six to eight hours, and on awakening the patients were immediately alert and free from headache, dullness or dizziness, which so often follows the administration of barbiturates. Of the 100 patients studied, the results were qualified as excellent to good in 54%, moderately good in 28%, mediocre in 12%, and as failure in 6%. Of the six failures, five were seriously ill patients in constant pain who had not responded to many other hypnotics.

Parsons and Thomson[9] carried out a double-blind study comparing methaqualone at two-dose levels, namely 150 mg. and 200 mg., cyclobarbitone 150 mg. and 200 mg., and a placebo. The conclusion from this investigation was that methaqualone is a reliable hypnotic, and no important difference could be detected between the hypnotic action of 150 mg. methaqualone and 200 mg. of cyclobarbitone.

The present investigation was undertaken to extend these studies.

METHOD

The double-blind technique was used. Identically appearing capsules were prepared containing either 150 mg. of methaqualone,* 100 mg. of secobarbital, or lactose (placebo). The letters A, B or C were the only identifying marks on the label; and physicians, nurses and patients were unaware of which bottles contained the active ingredients or placebo.

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*Supplied by Charles E. Frosst & Co., under the trade name "Mequelon".

One hundred and five hospitalized patients (51 males and 54 females) in the public wards were the subjects for this study. The average age of the entire group was 45 years (range 14 to 81). The only criterion for selection was that they had been receiving a hypnotic to aid them to sleep for some time. In order to avoid error, all patients in the group received the same preparation one-half hour before retiring. The preparation administered was changed every five days. All three preparations were received by 28 patients; 40 received two preparations, and 37 received only one.

At the end of the study the code was broken and it was found that preparation A, the placebo, was dispensed 303 times; preparation B, methaqualone, 332 times; and preparation C, secobarbital, 310 times. The same observer classified all the results, awarding a poor, fair or excellent mark based on promptness of induction, duration and quality of sleep, number of awakenings during the night, and the general condition of the patient in the morning.

RESULTS

There was a significant statistical difference between the results achieved by the placebo and by the hypnotics. The chi square value, calculated from the data in Table I, is 162; the probability of chi square on the 0.001 scale is 18.5.[10]

TABLE I.

Medication	*Results*			
	Mediocre	*Good*	*Excellent*	*Total*
Placebo (A).....	82	104	117	303
Methaqualone (B)..	23	63	246	332
Secobarbital (C)...	9	48	253	310
Total.....	114	215	616	945

Thirty-eight per cent of the patients receiving the placebo slept well as compared with 74% excellent results for methaqualone and 81% for secobarbital. Of 114 poor results, 72% followed the placebo, 20% methaqualone, and 8% secobarbital.

It should be noted that 15% of the patients were receiving tranquillizers, but since these were fairly evenly distributed among the three series, no account of this was taken in assessing the results. The hypnotic side effects such as fatigue, drowsiness, heaviness and headache were observed in 35 instances. It is of interest that the majority of these, 40%, were reported by patients after the placebo, 37% after secobarbital, and 23% after methaqualone.

No noteworthy differences were observed between the effects of the two hypnotics as far as promptness of induction and duration of sleep were concerned.

Hepatic function studies were made in 15 patients at the end of treatment. All were within normal limits. Hematological studies were not carried out, since Bernard[11] had already shown that methaqualone produced no alterations in the blood picture.

SUMMARY

A brief review of the literature on the pharmacological and hypnotic effects of a new chemical compound, methaqualone, has been presented. A double-blind study comparing the hypnotic effects of 150 mg. of methaqualone, 100 mg. secobarbital and a placebo is reported.

Methaqualone proved to be an excellent night-time sedative in 74% of 332 administrations as compared with 81% of 310 secobarbital administrations and 38% of 303 placebo administrations.

No significant side effects were observed. In 35 patients in whom post-hypnotic fatigue, drowsiness, heaviness or headache occurred, 40% followed the placebo, 30% the secobarbital, and 23% the methaqualone. Methaqualone, a non-barbiturate hypnotic, appears to be a distinct contribution to the group of drugs useful for night-time sedation.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

It is evident that medicine has not lost its popularity as a profession in Ontario, and the classes in all the universities are as large, if not larger than ever; the University of Toronto leading with a first year class of one hundred and forty-four students: this too in spite of the raising of the matriculation standards.

The wonder is what is to become of these students when they graduate, and yet when the rapid growth of Canada is contemplated, it is evident that the supply will not be greater than the demand.

There is a feeling in university circles that in the near future the entrance standards must be raised still further, and it would not be surprising if in due course senior matriculation would be demanded.

When the newer provinces have established universities of their own, with properly equiped medical departments, it stands to reason that the eastern school will lose a marked number of students. More than ever then they must make their courses attractive to the best men if they are to flourish, and no doubt post-graduate work will also be developed as it has not been attempted in the past.—Editorial, *Canad. M. A. J.*, 1: 1206, 1911.