hyperchloraemic acidosis. Occasional instances have been reported in the still scanty literature, which has been reviewed elsewhere (Pyrah and Raper, 1955; Pyrah, Care, Reed, and Parsons, 1955), but such examples can sometimes be explained by collateral circumstances such as urinary obstruction. Biochemical investigations carried out in the Department of Urology at Leeds have shown, by a series of perfusion experiments using artificial urine, that chloride and sodium ions in almost equal proportions can pass across the mucous membrane of an isolated excluded bladder, and also across that of a bladder to which a loop of ileum has been joined, into the blood stream and also in the reverse direction: there is a small net uptake of both ions equally. Only in the case of potassium ions does there seem to be any danger: if in the fluid perfusing the ileum the potassium concentration is more than three times that in the blood plasma, the cellular potassium being normal, there is a net movement of potassium ions from the lumen of the ileum into the blood plasma. If kidney function is greatly impaired, an elevation of the blood potassium may result, which could be dangerous; with the average healthy kidney in the cases which we have operated on, however, we have not so far clinically detected, nor found biochemically, any dangerous rise of serum potassium (Pyrah, Care, Reed, and Parsons, 1955).

Conclusion

The cases which I have described demonstrate that a loop of lower ileum is suitable anatomically and physiologically for incorporation into the urinary tract. There appears to be little if any risk of hyperchloraemic acidosis, but further experience is needed before we can be completely happy about the absorption of potassium from the loop. The cases for which I have used an ileal loop have been very worth-while, in that troublesome symptoms such as frequency of micturition have been relieved, kidneys have been preserved which would gradually have deteriorated or would have had to be excised, and, finally, a procedure for a true artificial bladder, with micturition *per vias naturales*, has been developed. Further experience of more cases is needed before the final place of such operations in surgery can be assessed.

I wish to thank my colleague, Mr. F. P. Raper, for permission to include the description of Case 5.

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Daily visiting by mothers of their children in hospital, and assistance with their nursing, are now accepted as valuable in many hospitals. There remain a number, however, where there is little enthusiasm for the practice or even opposition to it. According to the annual report for the year 1954–5 of the Royal Alexandra Hospital for Children, Sydney, Australia, daily visiting was introduced into some of the wards of the hospital during the twelve months covered by the report. Difficulties arose in the larger wards of obsolete design, as there the sisters-in-charge were too busy to be able properly to supervise free visiting by the mothers. In the smaller wards, however, the scheme for daily visiting is progressing satisfactorily, and good understanding between the mothers and the nursing staff has been established. It is intended, the report states, to extend the scheme as far as possible.

CLINICAL TRIAL OF "DORIDEN," A NEW HYPNOTIC

WITH NOTE ON USE OF RANKING METHODS IN ASSESSING THERAPEUTIC EFFECT

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The clinical trial of a new hypnotic presents several difficulties. Tests in a general hospital are often unsatisfactory and difficult to plan, since in most cases sleeplessness diminishes as familiarity with new surroundings develops and the acute stage of an illness passes. Insomnia is common in the elderly, and the assessment of a hypnotic is clearly most valuable if it can be done while the patients are living at home. In such circumstances it is impossible to measure accurately either the time in getting off to sleep or the duration of sleep. Nevertheless, patients can usually make a definite statement on whether they have had a restful night, and can compare how they have slept on different occasions. Accordingly, if suitable precautions are taken a reliable assessment should be possible in a general practice.

A trial of α-phenyl-α-ethyl glutarimide ("doriden") has been attempted under such conditions. Animal experiments had not demonstrated any serious toxic effects (Gross, Tripod, and Meier, 1955). Preliminary observations, in which single doses of either 0.25 g. or 0.5 g. of doriden were given, suggested that the larger amount produced approximately the same effect as 0.2 g. of cyclobarbitone. The results of Lanz (1955) and of Müller and Rohrer (1955) also provided evidence that 0.5 g. of doriden was a suitable hypnotic dose. The investigation was designed in two parts. In the first place a controlled trial of the action of the drug as a hypnotic was carried out, and, secondly, the effect of courses of doriden was studied both in hospital and in general practice, with particular reference to the development of undesirable or toxic features.

Design of Trial

Twenty patients living at home agreed to take part in the trial. The experimental design required a multiple of six subjects, 18 being a convenient number, and the two additional patients were kept in reserve. They had all previously been taking a barbiturate, and whenever attempts were made to stop this medication they complained of insomnia. Contributory factors in producing the insomnia in several patients were cough and rheumatic disorders. Cases in which pain rather than insomnia was the predominant feature were excluded. None of them was confined to bed during the day. In view of the difficulty in determining the real necessity for a hypnotic in many patients, it was considered essential to include a placebo in the trial. Accordingly the action of doriden has been compared with the effect of cyclobarbitone and of an inert tablet.

Doriden, 0.5 g., cyclobarbitone, 0.2 g., and inert tablets were prepared so that they were identical in appearance.

All contained 3.6 mg. of quinine sulphate, so that their taste was similar and the barbiturate, which might otherwise be recognized, could not be distinguished. Three tablets of each preparation were placed in three separate envelopes. Each patient was given a code letter and envelopes were numbered 1, 2, and 3. The tablets of envelope 1 were taken on three successive nights, and thereafter the tablets of envelopes 2 and 3, so that the trial extended over nine nights. It was arranged that equal numbers of patients received the preparations in the six possible orders. The allocation of code letters to patients was at random. The clinical assessors knew that different preparations were being used but were unaware of the order in which they were given. The patients were not told the composition of the tablets, but were asked to assess the relative hypnotic effect of the contents of the three envelopes. They were given a form on which they recorded, the morning after taking each tablet, approximately how long it had taken them in getting off to sleep, how long they had slept, whether they had had a restful night, and whether they had had any after-effects. On this basis they were requested to put the envelopes in order of preference. The patients were visited after three nights to make certain they understood and were carrying out the instructions. The completed forms were collected after the final night and any additional clinical observations were noted. The order of treatment was not revealed until all assessments in each patient were completed.

Results

One of the first 18 patients did not complete the trial as she felt giddy after taking the first tablet (which afterwards was found to be a placebo) and was unwilling to continue. The nineteenth patient accordingly took her place. The ranking given by the patients to the different tablets is shown in Tables I and II. Analysis of the results shows a highly significant measure of agreement between the patients. This agreement is demonstrated in the statistical appendix to result from the superiority of either drug over the placebo, there being no significant difference between the two drugs in the conditions of the trial. Most of the patients had no difficulty in deciding their order of preference, though one was unable to differentiate between doriden and cyclobarbitone. Fourteen (78%) put the placebo in third place. Ten (56%) chose doriden for first place and six (33%) cyclobarbitone.

TABLE I.—*Comparison of the Hypnotic Effect of Doriden*, 0.5 g., *Cyclobarbitone*, 0.2 g., *and of an Inert Tablet*

Code Letter	Sex and Age	Weight (kg.)	Ranking			Order of Test	Previous Treatment	After-effects
			D.	C.	P.			
A	F 81	77	1	2	3	D.P.C.	C. 0·27 g.	None
B	M 76	61	1	2	3	P.C.D.	B. 0·2 g.	Headache on 1 morning after cyclobarbitone
C	F 83	64	1	2	3	P.D.C.	Ph. 0·06 g.	None
D	F 84	55	2	3	1	C.D.P.	C. 0·2 g.	,,
E	F 72	67	1	2	3	D.C.P.	Ph. 0·06 g.	Drowsy on 2 mornings after cyclobarbitone and on 1 morning after doriden
F	F 72	66	2	1	3	C.P.D.	C. 0·2 g.	None
G	M 69	88	2	1	3	P.D.C.	B. 0·2 g.	,,
H	F 78	43	2	1	3	C.P.D.	S.A. 02·g.	Nausea on 3 mornings after doriden
I	F 52	62	1	3	2	D.P.C.	,, ,,	Drowsy on 3 mornings after cyclobarbitone
J	M 77	73	2	1	3	D.C.P.	Ph. 0·06 g.	None
K	F 71	70	1	2	3	P.C.D.	C. 0·2 g.	,,
L	F 81	52	3	1	2	C.D.P.	,, ,,	Drowsy on 2 mornings after cyclobarbitone
M	F 54	53	1	3	2	C.P.D.	Ph. 0·06 g.	Drowsy on 3 mornings after doriden
N	F 53	38	1	2	3	D.C.P.	,, ,,	None
O	F 79	64	1	2	3	P.D.C.	C. 0·2 g.	,,
P	F 64	61	1	2	3	C.D.P.	,, ,,	Headache on 1 morning after doriden
Q	F 72	57	2	1	3	D.P.C.	B. 0·2 g.	None
R	F 82	57				P.C.D.	C. 0·2 g.	Felt giddy after taking one placebo tablet and abandoned trial
S	F 52	61	1·5	1·5	3	P.C.D.	Ph. 0·3 g.	None
Total of ranks			26·5	32·5	49			

Coefficient of concordance = 0·419. Snedecor's F. = 12·12. 1% level of F. = 5·7.

B. = Butobarbitone. C. = Cyclobarbitone. D. = Doriden P. = Placebo. Ph. = Phenobarbitone. S.A. = Sodium amylobarbitone.

TABLE II

Numbers Preferring Doriden to Cyclobarbitone, and vice versa

Order of Administration	No. Preferring Doriden	No. Preferring Cyclobarbitone
Doriden before cyclobarbitone	6	3
,, after ,,	5	3
Total	11	6
Expected	8·5	8·5

Numbers Ranking the Placebo Third

Order of Administration	No. Ranking Placebo Third	No. Not Ranking Placebo Third
Placebo first	6	0
,, second	4	2
,, third	4	2
Total	14	4
Expected	6	12

The tablets were taken immediately before preparing to go to bed. The estimates of the times in getting to sleep after taking the three different treatments were: doriden, 71 ± 8.5 minutes (s.e.); cyclobarbitone, 84 ± 10.7 minutes: and placebo, 138 ± 20.8 minutes.

It was impossible to make any satisfactory analysis of the duration of sleep. In many cases, particularly after the placebo, there were intermittent periods of wakefulness and restlessness which could not be estimated, and treatment in many instances affected the quality rather than the quantity of sleep. Nevertheless, on studying the reports it was clear that relief of this restlessness was one of the most important considerations of the patients in deciding on the ranking.

Drowsiness on the following morning was noted on seven occasions after cyclobarbitone and on four occasions after doriden. These differences are not significant ($\chi^2 = 0.91$, $n = 1$, $P > 0.05$). One patient complained of nausea on the three mornings after doriden but not on the other mornings. No other definite after-effects were noted.

The patients up to the time of the trial had been receiving a barbiturate. As it is possible that they might have become habituated to this, the influence of the order of taking the drugs on the patients' assessment was examined. The details of this analysis are described in the Appendix. However, no correlation was found to exist.

After completion of the trial doriden was given as a hypnotic to 30 patients, either in hospital or in general practice. The length of the courses varied from 3 to 80 days and the dose was either 0.25 or 0.5 g. at night. No definite evidence of habituation or tolerance was obtained. In two patients a skin rash developed. This was widespread over the trunk and limbs, erythematous, and irritating. It disappeared within two days after discontinuing the drug. In one of these patients doriden was resumed four days later and there was no recurrence of the rash during a further period of 40 days. In one patient with treated thyrotoxicosis and congestive cardiac failure, mental excitement and confusion developed 1½ hours after giving 0.5 g. doriden and persisted for about three hours. A second dose of doriden was given four days later with a similar result. No other definite side-effects have been observed with doriden.

Discussion

The main conclusions of this investigation have been based on ranking methods, whose use is further discussed in the statistical appendix. Such methods have one great disadvantage in that different judges may be ranking the same items according to different subjective criteria. This is a particular danger in clinical trials, where it is clearly possible that factors other than pharmacological action may influence the patient. For this reason the order of administration of the different drugs must be randomized, irrelevant considerations such as size or flavour of tablet must be eliminated so far as is possible, and the order of administration of the different drugs must be concealed from all concerned. Since these three precautions were taken in the trial described above, the results are thought to have objective validity.

In the ranking trial although doriden, 0.5 g., was adjudged by a small majority to be superior to cyclobarbitone, 0.2 g., the difference in mean ranks was not significant. The inert tablet, however, was put in third place by a large majority and its mean rank differed significantly from those of the two drugs. In interpreting this result certain possible sources of error must be considered. The optimal dose of cyclobarbitone may not have been used, though this is the commonly prescribed amount. The incidence of drowsiness on the following morning after this dose was 13% ; a smaller dose might have found more favour. Doriden may have unduly benefited from the previous prolonged barbiturate medication. Statistical analysis failed to detect any significant effect of this nature during the period of the trial (see Appendix), but this finding does not entirely exclude the possibility of its existence. The latter could be done only by repeating the trial after an equally long period of doriden administration.

Doriden clearly has a reliable hypnotic action, relatively rapid in onset and not unduly prolonged. The main disadvantage is the occasional production of a skin rash, though nausea and possibly mental excitement may also be infrequent complications. A non-barbiturate hypnotic would be of some value, but the ultimate place of doriden in therapeutics will depend on the frequency of these undesirable effects, and this can be determined only by prolonged investigation.

Appendix: Statistical Analysis of Results, with Special Reference to the Use of Ranked Data in Therapeutic Trials

Ranking methods have not been used extensively in clinical trials, but they are of considerable value in assessing the relative merits of drugs, especially those designed to give symptomatic relief. In using agents of this type it is often difficult to make exact objective measurements of the effects, while the patients are able to make definite statements and comparisons regarding the relief they have obtained. The ranked data of this trial represent not objective measurements but subjective judgments. The relevant tests of significance are based in general on the frequency with which one item is ranked above another by a panel of judges. Each object judged causes a psychological reaction which can be thought of as a point on a psychological continuum. It must be assumed that reactions to the same item are normally distributed on this continuum. A comparison of two items thus consists in a comparison of two such reactions, the strength of each of which varies about its mean according to the normal probability law. Owing to this distribution, if two items produce a psychological reaction of exactly the same mean strength, half the judgments would be expected to rank one object first, while the remaining half would rank the other first. In practice, a certain number of ties would occur owing to the lack of accuracy inherent in subjective estimates. A difference in the mean strength of their respective psychological reactions causes one item to be judged better than another more than 50% of the time.

Moroney (1953) describes in elementary terms some statistical methods applicable to ranked data. A more advanced treatment is given by Kendall (1948), while Guilford (1950) describes conversion of ranked data to scores on a continuous scale. Ranking methods have, however, a sound mathematical basis independent of any underlying scale, and conversion of ranks to measurements on a continuum should be used only if there is no appropriate ranking method available.

The coefficient of concordance, W, measures the degree of agreement between a number of judges assessing a series of items in order of preference. It was calculated from the figures of Table I, according to the formula (Moroney, 1953, p. 338) :

$$W = \frac{12S}{m^2(n^3-n)}$$

where S = sum of squares of deviations of the observed rank totals from the average rank total (the latter would be the expected value in all cases if there were no difference between the items ranked) ; m = number of judges ; n = number of items to be judged. Subtracting 1 from S and adding 2 to $\frac{m^2(n^3-n)}{12}$ as a continuity correction, Snedecor's F is then given by

$$F = \frac{(m-1)\,W_{corr}}{1-W_{corr}} = 12.12$$

Entering tables of F at $n-1-\frac{2}{m}=18/9$ degrees of freedom for the greater variance estimate and $(m-1)(n-1-\frac{2}{m})=32\,1/9$ degrees of freedom for the lesser variance estimate, the value for the 1% significance level is 5.7. Hence there is a significant degree of concordance between the judges. Kendall (1948) gives a table of significant points of S for values of m from 3 to 20 and n from 3 to 7. He also describes other methods of estimating the significance of observed values of W. Since the two drugs were compared with a placebo it is possible that the difference between taking a drug and not taking a drug is alone responsible for the agreement between judges. The significance of the difference between the doriden and cyclobarbitone figures must consequently be tested. Furthermore, the fact that the subjects took barbiturates regularly before the experiment makes it possible that they had become habituated to this drug and might underestimate the efficacy of cyclobarbitone relative to doriden, which is not a barbiturate. This habituation effect should decrease fairly rapidly if the administration of the drug is discontinued. It follows, therefore, that if barbiturate habituation were present cyclobarbitone would appear relatively more effective if given earlier.

The χ^2 test can be applied to the numbers preferring one drug to another and to the numbers ranking the placebo third (see Table II), in which the ideal values which would be expected on the basis of the respective null hypotheses are also given. For the preference between drugs, χ^2 = 1.5, which is not significant. For the numbers giving the placebo third rank, χ^2 = 18.06, which is significant at the 0.1% level. Hence both drugs are superior to the placebo, but there is no evidence in favour of one drug against the other. There is, furthermore, no evidence worth testing of any relation with order of administration.

Ranking methods, such as those described here and elsewhere, are likely to prove useful in certain types of therapeutic trial. Although they are simple to apply, the fact that they are based on subjective judgments makes rigid experimental control necessary if satisfactory results are to be obtained.

Summary

A new hypnotic, α-phenyl-α-ethyl-glutarimide ("doriden") was investigated in a general practice using ranking methods, and its effect was compared with that of cyclobarbitone and an inert tablet. In a dose of 0.5 g. it compared favourably with cyclobarbitone, 0.2 g.

Occasional toxic effects are described. Some statistical considerations in the use of ranking methods are appended.

We should like to thank Dr. C. D. Falconer, of Ciba Laboratories, for his assistance in arranging the supply of the tablets, and Dr. G. H. Jowett for his advice on the statistical analysis.

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FURTHER EXPERIENCE WITH AMIPHENAZOLE AND MORPHINE IN INTRACTABLE PAIN

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In a recent paper (Shaw and Shulman, 1955) it was shown that the combination of large doses of morphine (1–2½ gr., 65–160 mg.) with amiphenazole (D.A.P.T.; "daptazole") resulted in the alleviation of the intractable pain of terminal carcinoma. Since the publication of that paper the treatment has been used in further cases. The same total relief has been achieved in almost all the additional cases (127). Further evidence has accumulated that demonstrates the complete harmlessness of amiphenazole.

Present Series

Amiphenazole is one of a series of compounds which have been shown to arouse dogs deeply narcotized with morphine and hyoscine (Shaw and Bentley, 1955). In humans it counteracts the morphine-induced respiratory depression, vomiting, narcosis, and depression of the cough reflex without affecting the analgesia. The drug may also alleviate the constipation associated with the continued administration of morphine. We have observed the "pin-point" pupil of morphine in only one of our patients, although doses of 3½ gr. (217 mg.) have been given. Twenty patients have received large daily doses of morphine for periods of four to eight months without any evidence that tolerance has developed. In five cases it has been necessary to increase the dosage of morphine by 100%; in most instances the necessity for this increase could be accounted for by the increasing severity of the pain.

An unexpected outcome from the present series has been the bright mental outlook shown by three-quarters of these otherwise hopeless cases. Before treatment the subjects were all suffering moderate to severe pain and exhibited various degrees of depression. After about two weeks' treatment a remarkable change in the outlook of about 75% was noticeable. They took a renewed interest in the life of the ward, in occupational therapy, or in hobbies. Such a psychological improvement was noticed not only by the nursing staff but by the relatives. It would, of course, be possible to ascribe these effects to the euphoric action of the morphine. The uplift did, however, markedly decrease when the patients still received morphine without the amiphenazole, and restitution of the amiphenazole after two weeks' deprivation again resulted in a mental improvement.

We feel that it can be said with some certainty that the improved mental outlook was due to the amiphenazole and not to the morphine, for the following reasons. When the use of amiphenazole was discontinued in the presence of large doses of morphine there was an interval of two to three days before depression and sleepiness set in. On restitution of the amiphenazole improvement in outlook took place within 24 hours. Several patients on 60 mg. of amiphenazole had to have their dosage reduced to 20 mg. because they had too much insight into their condition.

These findings of mild central stimulation provoked us to try the drug alone in cases of depression not associated with pain. The results showed remarkable promise. The series is, however, too small to enable one to draw conclusions. This work is proceeding and the results will be published later.

In the earlier paper (Shaw and Shulman, 1955) the possibility of toxic reactions from the use of amiphenazole was cautiously discussed. The main untoward feature was a mild untroublesome mental confusion in some of the aged patients. We were unable to decide whether to ascribe this to the large amounts of morphine or to the amiphenazole. It has not been observed in patients below the age of 55. The harmlessness of amiphenazole has been shown by the repeated administration of up to 300 mg. intravenously to healthy volunteers. This dose produces neither subjective symptoms nor any objective changes in blood pressure, heart rate, or respiration. (The usual therapeutic dose is 20–40 mg. orally.) We are indebted to Dr. Gershon for assistance in this matter. Chronic toxicity tests in animals are in progress, with, after four months, negative results. These tests are continuing.

Method of Treatment

Although in our series of over 127 cases we have not encountered a patient sensitive to morphine, we approach the use of large doses of that drug with caution. The patient will usually be receiving ¼ or ½ gr. (22 or 32 mg.) of morphine before treatment is started. The patient is then given doses of morphine which increase by increments of ¼ gr. (16 mg.) and 20–30 mg. of amiphenazole. It is permissible to mix the solutions in the one syringe, and the injections may be made intramuscularly or hypodermically. The injections are repeated when pain returns. The morphine increments are continued until the analgesia is complete for six to eight hours (it is not necessary to increase the dose of amiphenazole). The patient is then said to be stabilized. In cases of moderate pain stabilization will be reached with doses of 1–1½ gr. (65–95 mg.) of morphine (with 20–30 mg. of amiphenazole). Severe pain will require up to 3 gr. (195 mg.) of morphine at a single injection.

When the patient is stabilized (in about two days) the intramuscular injection of amiphenazole is replaced by oral administration. The oral dose will vary with the circumstances. As we have said, amiphenazole counteracts the sedative effect of morphine and may itself have a slight stimulant effect. Accordingly, in most patients it is possible to control the degree of alertness by increasing or decreasing the dose of amiphenazole given during the day. The range of oral dosage is 20–60 mg. In the evening and at night it is advisable to reduce the dose to 20 mg.