as that described above, while the other had capillary damage without alteration in the platelet count. The thrombocytopenia of the first was clearly shown to have been due to carbutamide, and an unusual feature in her case was the very rapid rise in the platelet count when the administration of the drug was stopped. This is strongly suggestive of peripheral destruction of platelets rather than of a toxic effect on the marrow, though *in vitro* evidence of sensitization was lacking. It is noteworthy that both patients had shown signs of intolerance, in the form of allergic skin manifestations, some time before the purpura appeared.

These two patients were later given tolbutamide. The patient who had developed thrombocytopenic purpura while receiving carbutamide showed a slight but significant fall in the platelet count when tolbutamide was given, but there was no further fall while the administration of the drug was continued, and Hess's test remained negative. There was therefore no good evidence that sensitization to carbutamide had produced cross-sensitization to tolbutamide. On the other hand, the patient who had developed non-thrombocytopenic purpura *one month* after the administration of carbutamide had been resumed, following its long interruption, developed purpura again after she had been receiving tolbutamide for *one month*. No conclusions can safely be drawn from these isolated findings, but they at least suggest that though tolbutamide is not a sulphonamide its toxic actions may be similar to those of carbutamide.

An effect of carbutamide on the capillaries was seen. In many patients capillary resistance was found to be increased when the administration of carbutamide was stopped, even when the platelet count had been high. The point was not fully investigated, but it seems probable that carbutamide accentuates the increased capillary fragility which is due to the diabetes itself. When the antigenic similarity of platelets and capillary endothelium is borne in mind, this is an understandable effect of a drug which has been shown to cause thrombocytopenia. It is clearly an unwelcome attribute, for such diabetic complications as retinopathy and nephropathy will presumably be influenced adversely. It must, however, be emphasized again that these observations were not adequately investigated, and require confirmation.

The toxic effects of carbutamide on the blood are therefore those which might have been anticipated in the extensive use of any sulphonamide. However, when in a group of only 40 patients it has been possible to show so many instances of harmful effects on the white cells and the blood platelets, it is obvious that the drug is dangerous. Added to this, there is the possibility that it may accentuate any damage to small blood vessels. Carbutamide cannot be regarded as a safe substitute for insulin in the routine control of diabetes.

Summary

A haematological study was made of 40 patients who were receiving carbutamide for the control of diabetes mellitus. Leucopenia was common soon after this treatment was instituted, but usually the white-cell count rose again as the administration of carbutamide was continued: one patient, however, developed a severe leucopenia which persisted until treatment was discontinued.

Many patients showed a mild depression of the platelet count, and two developed spontaneous purpura. In one case the purpura was thrombocytopenic, and was shown conclusively to have been due to carbutamide. In the other the purpura was non-thrombocytopenic, and was probably due to carbutamide. Both these patients were later given tolbutamide, and the possible toxic effects are discussed.

Clinical observations suggested that carbutamide accentuates the increased capillary fragility which may occur in diabetes, but this point was not fully investigated and the findings require confirmation. It is concluded that carbutamide is not a safe drug for use in the routine control of diabetes.

I wish to thank Professor D M. Dunlop for his encouragement and advice, and I am indebted to him and to Drs. Joyce D. Baird and L. J. P. Duncan for giving me the opportunity of carrying out these investigations on their patients.

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EFFECTS OF "PACATAL" ON SYMPTOMS IN CHRONIC PSYCHOTIC FEMALE IN-PATIENTS

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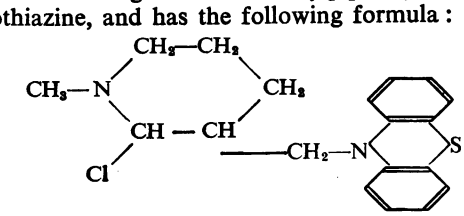
"Pacatal," or pecazine, is one of eight different ring derivatives of phenothiazine synthesized by Schafer and Nezel in Hamburg. It is N-methylpiperidyl-(3)-methylphenothiazine, and has the following formula:



It was tested in animals by Nieschulz *et al.* (1954) and found to be well tolerated and to have various actions, including a tranquillizing effect on all animals, with somnolence in larger doses; an antisympathetico-mimetic reduction of blood pressure; a potentiation of analgesics and narcotics; and an antiperistaltic action. Werenberg (1955), from whom the above information is derived, describes other effects of the drug in animals.

The therapeutic investigation described in this paper was devised in an attempt to determine whether pacatal was effective in the control of certain symptoms in chronic psychotic female patients—namely, incontinence, aggression, and noisiness—without the toxic side-effects which have sometimes caused anxiety when chlorpromazine, another phenothiazine compound, has been used.

Method

For the purpose of the investigation, 76 female patients suffering from chronic psychosis, of age range 32 to 75 years (average 59.5 years), were accommodated in one large ward. They were all long-stay patients, the duration of hospitalization ranging from 6 to 46 years (average 21 years). All were regressed in varying degrees and none had received any recent significant treatment. Most were suffering from schizophrenia (Table I).

TABLE I.—*Age and Diagnosis Distribution of the Groups*

		Pacatal	Control
No. of patients		37	38
Age	Minimum	32 years	35 years
	Maximum	75 ,,	74 ,,
	Mean	59·5 ,,	59 ,,
Diagnosis on admission	Schizophrenia	26	26
	Manic-depression	9	4
	Others	2	8
Duration in hospital	Minimum	6 years	10 years
	Maximum	42 ,,	46 ,,
	Mean	19·5 ,,	23·3 ,,

The patients were divided into two clinically random groups, which were, as Table I shows, similar in age and diagnostic distribution. The patients in one group received throughout the experiment active tablets of pacatal, for the first 12 days of the trial, in a dosage of one tablet three times daily (75 mg. daily); for the next 28 days two tablets three times daily (150 mg. daily); and for the final 12 days three tablets three times daily (225 mg. daily). Thus each patient in this group received a total of 7.8 g. of pacatal. The patients in the other group received equal numbers of inert control tablets which were identical in appearance with the active tablets. The identity of the tablets was known only to the hospital pharmacist.

For statistical purposes, with one exception (a patient in the pacatal group who had to be moved out of the ward for administrative reasons) those patients who were unable to complete the course of active tablets were regarded as having done so.

In an effort to make the investigation as objective as possible, only three symptoms were recorded throughout; the numbers of incidents of incontinence, aggression, and noisiness being recorded by the nursing staff against the patients' names on a large wall chart. Incontinence, either urinary or faecal, is self-explanatory. Aggression was defined as striking another individual or attempting to do so, and noisiness as a vocal outburst sufficient to warrant segregation of the patient because of her disturbing effect on other patients.

In addition, the blood pressure of each patient was recorded twice weekly by two of us (A. K. and P. S.), on each occasion at the same time of day, without change of instrument, posture, or investigator. At the same time any toxic effect was looked for and recorded. Apart from this, no detailed clinical appraisal of the patients was attempted, either before or during the investigation.

Results

Control of Symptoms.—Thirty-seven patients received pacatal and 38 were controls. In the pacatal-treated group there were 61 occurrences of incontinence, 31 aggressive acts, and 101 noisy outbursts, compared with 145, 96, and 206 respectively in the control group. In each case the difference is significant beyond the 1 in 20 level of probability. Thus there are significantly fewer incontinent, aggressive, or noisy incidents in the pacatal-treated group than in the control group.

Statistical Method.—In each case the incidence of acts of incontinence, aggression, or noisiness is expressed as a proportion of a hypothetical normal, this being the number of acts that would have occurred if each patient had been incontinent, aggressive, or noisy once weekly. The difference between the proportions so determined in the two groups is then compared with its standard error (Table II). As a further control, the rates of occurrence of the three symptoms in the first 26 days of the investigation were compared with those in the second 26 days. In the group receiving pacatal the rates of incontinence and noisiness were significantly less in the second than in the first period, and that of aggression less, but not significantly so. In the control group there was no significant difference in the rates of incontinence. The rate of aggression showed an increase which just failed to be significant, while the rate of noisiness showed a significant increase in the second half of the period (Table III).

TABLE II.—*Symptomatic Incidents in Groups, With Statistical Analysis*

	Pacatal-treated Group	Control Group	Difference Between Rates	Standard Error Difference
No. of patients	37	38		
Incontinent incidents	61	145		
Rate of incontinence (% if each patient incontinent once weekly)	22	51·5	29·5	10·6
Aggressive incidents	31	96		
Rate of aggression, %	11·3	34·0	22·7	10·7
Noisy incidents	101	206		
Rate of noisiness, %	36·7	73	36·3	10·6

TABLE III.—*Comparison of Symptomatic Incidents in First and Second 26 Days of Treatment*

	Number of Incidents		Rates % of 1 Incident per Patient per Week		Difference in Rates %	Standard Error of Difference
	1st 26 Days	2nd 26 Days	1st 26 Days	2nd 26 Days		
Incontinence:						
Pacatal group	50	11	36·4	8·0	28·4	9·1
Control ,,	75	70	53·1	49·6	3·5	11·5
Aggression:						
Pacatal group	23	8	16·7	5·8	10·9	7·2
Control ,,	34	62	24·1	43·9	19·8*	10·6
Noisiness:						
Pacatal group	72	29	52·4	21·1	31·3	10·6
Control ,,	84	122	59·5	86·4	26·9*	9·9

* Increase.

Toxic Complications

Serious toxic complications of three types—jaundice, hypotonia, and neutropenia—occurred in a total of 16 (43%) of the patients receiving pacatal (Table IV).

TABLE IV.—*Analysis of Toxic Effects in 37 Pacatal-treated Patients*

		Jaundice	Neutropenia	Hypotonia	Total
No. of cases		2	4*	10	16
% of total		5·4	10·8	27	43·2
Age	Minimum	43 years	49 years	35 years	35 years
	Maximum	56 ,,	63 ,,	74 ,,	74 ,,
	Mean	48·5 ,,	58 ,,	59·4 ,,	57·8 ,,
Drug taken	Minimum	1·5 g.	6·8 g.	2·9 g.	
	Maximum	3·9 ,,	7·8 ,,	7·3 ,,	
	Mean	2·7 ,,	7·2 ,,	5·6 ,,	

* Includes one fatal case.

Jaundice.—Two patients developed mild jaundice; one after taking 1.5 g. and the other after 3.9 g. of pacatal. Both recovered spontaneously after withdrawal of the drug.

Hypotonia.—Ten patients developed a state of unilateral hypotonia. All showed a similar picture, differing only in degree. The syndrome consisted of a marked flaccidity of the extensors of both limbs of one side of the body and a concomitant flaccidity of the ipsilateral erector spinae muscles. The patients walked with semiflexed arm and leg, tilting to the hypotonic side. All had unsteady gait, two to such an extent that they fell, injuring themselves. Because of mental regression, detailed neurological examination was difficult, but it appeared that co-ordination was normal apart from the effects of the hypotonia. Those able to understand the

instructions could perform the finger–nose test with accuracy and without tremor. There was no nystagmus or signs of extrapyramidal or pyramidal motor lesions. Sensory examination was impossible because of the mental state, but there did not appear to be any posterior column involvement, gait being co-ordinated, allowing for the abnormal posture. One case of this condition occurred after 2.9 g. of pacatal; then towards the end of the trial nine cases occurred within a few days. The first case continued to receive pacatal to the end of the trial without any worsening. After withdrawal of the drug all cases recovered within seven days.

Neutropenia.—Four patients developed neutropenia late in the trial. In the first case, a woman of 61 presented with a small local infection of the thumb and, despite blood transfusion, penicillin, and cortisone, died of agranulocytosis 15 days later. The remaining three cases which were detected by routine white-cell counts, all occurred after the administration of between 7 and 7.8 g. of the drug. Two showed white-cell counts of 3,500 per c.mm., with 40% neutrophils. Pacatal was immediately withdrawn and the blood counts returned to normal within seven days. In the fatal case and one of the others, bone marrow biopsy confirmed an agranulocytic reaction.

Minor toxic effects in the patients receiving pacatal included dryness of the mouth and disturbances of vision, but these were not serious enough to seriously inconvenience or endanger the patients concerned and have not been tabulated.

Effect on Blood Pressure

It was found that many patients in both groups had labile blood-pressure recordings, sudden falls and equally rapid recoveries occurring at frequent intervals. Falls in the systolic pressure of 20 or more mm. Hg were recorded in 16.1% of the patients receiving pacatal and in 15% of the control group. The difference is not significant.

Discussion

The necessity of subjecting any new drug to adequate controlled clinical trials, so that its field of usefulness can be exactly determined before it is used generally, has been recently stressed (*British Medical Journal*, 1956). At the same time, psychiatric investigations present particular problems of objectivity, quantitative measurement, and adequate controls. It seems that a measure of the number of occurrences of particularly easily detected symptoms is one relatively simple way of meeting these difficulties (Mitchell, 1956). By this means, patients taking a new drug can continue to live in the same environment as previously, as they are not subjected to unusual prolonged clinical interviews by medical staff or others. Measurement of symptoms becomes a simple recording on a wall chart of each episode (in this investigation) of incontinence, noisiness, or aggression. As the individuals in a clinically similar and numerically equal control group, given an identical-appearing tablet, have similar recordings taken it is not necessary for every occurrence of a symptom to be recorded, as the final analysis is one of the relative frequency of each symptom. Thus there is a minimal change in environment, such change as there is being identical in control and the test groups, and it can be claimed that numerical differences observed in the objectively recorded symptoms are due (subject to statistical analysis) to the drug administered.

It might be argued that an initial observation period in all groups, prior to the administration of any active tablets, might have been desirable in reducing still further the effect of chance in the rather small clinically random groups chosen. It was felt, however, that the enthusiasm of the observers, on whom the success of the investigation depended, might quickly wane without positive results, so it was decided instead to compare incidences in the first half of the experiment with those in the second half as an additional statistical control, for not only were the patients on a bigger daily dosage of the drug in the latter part of the investigation, but it was presumed that pacatal, like chlorpromazine, would show some delay in developing its full effects. It was interesting that the control groups showed an increase in aggressiveness and noisiness, due, presumably, to increasing reluctance to take tablets.

It must be noted here that no attempt has been made to restrict the investigations to patients with one type of psychosis, though, as might be expected, despite the diagnosis distribution (on admission) as shown in Table I, nearly all were suffering from chronic schizophrenia. Whatever the diagnosis, the symptoms chosen for enumeration are those which make the nursing of the chronic regressed patient a difficult and often thankless task. Any drug which will safely help to make the patients more accessible, by reduction of these symptoms, is thus of great value in these days of serious nursing shortages.

Our findings concerning the effectiveness of pacatal in the control of these symptoms—incontinence, noisiness, and aggressiveness—are similar to those reported by Werenberg (1955) in an uncontrolled experiment. It seems likely that the significant reduction in the incidence of incontinent acts may well be due, in part at least, to the inhibitory action of the drug on the smooth muscle of the intestine and bladder, rather than to increased co-operation on the part of the patient.

It has already been reported by many observers that another phenothiazine compound, chlorpromazine, is effective in the control of turbulent chronic psychotic female patients (Elkes and Elkes, 1954; Andermann and Lindsay, 1955), but, as already stated, toxic side-effects occur with this drug. These, though not usually serious, often give trouble and have been widely reported. Lomas *et al.* (1955) give a very full account of them. Jaundice, dermatitis, and Parkinsonism are the most troublesome; but Pollack (1955) describes one fatal case of agranulocytosis in 500 patients treated with chlorpromazine. At Lancaster Moor Hospital we have found that skin sensitivity to chlorpromazine amongst the female nursing staff has been our greatest cause of anxiety. No fewer than 21 female and 2 male nurses who have handled the drug have developed dermatitis, which in some cases has been of long duration. Moreover, the sensitivity appears to be long-lasting, four of the female nurses showing strong reactions to patch testing nine months after the original attack (Seville, 1956).

Unfortunately, in this investigation, pacatal has proved to be even more toxic than chlorpromazine—so much so that the investigation was terminated prematurely. The occurrence of one fatal case of agranulocytosis and three cases of neutropenia in the relatively small number under treatment, apart from the postural complications already described, made it unjustifiable to continue.

Toxic complications of the drug have previously been described. Thus Werenberg (1955) found seven cases of leucopenia in his series of 100 patients undergoing treatment with pacatal, including one fatal case of agranulocytosis in a woman of 46 who also suffered from mild diabetes mellitus. She had had a total of 7.5 g. of the drug. Of the other six cases, one had to have the drug discontinued, the remaining five exhibiting a return of the blood count to normal without stopping the drug. A case of fatal agranulocytosis, not firmly established as due to pacatal, has also been described by Wenderoth and Lennartz (1955) after a total of 13 g. of the drug. C. S. Parker (1956, unpublished communication) reports one fatal case of agranulocytosis in a patient receiving pacatal.

Kline and Jacob (1955) described five cases of postural difficulty apparently similar to those found in this investigation. Because of this and other complications, they found it impracticable to continue giving the drug. In our series it will be noted that almost 25% of the patients developed postural difficulties, two severely. Although the symptoms resolved rapidly on termination of the drug, it is clear that they could prove serious and incapacitating to an outpatient undergoing treatment.

There do not appear to be any reports in the literature of jaundice occurring in patients undergoing pacatal therapy, other than those found in this experiment.

Other serious toxic effects in patients taking the drug have been described by Kline and Jacob (1955), three of whose group developed atonic bladders and bowels when on intramuscular therapy. One of these actually showed symptoms of an autonomic bladder and required catheterization.

Finally, Werenberg (1955), in his series, reports three further deaths: one apparently from cardiovascular collapse; one from embolism of the pulmonary artery, thrombosis of the common iliac vein, and myocardial degeneration, associated with severe constipation; and the third from embolism of the pulmonary artery and thrombosis of the plexus parametrialis together with a large uterine fibroma.

On the other hand, Bowes (1956) reports no serious toxic results in a series of 50 cases, some of whom received up to 600 mg. of pacatal daily.

However, the findings of Werenberg (1955), of Kline and Jacob (1955), and of the present investigation suggest that pacatal should be used only with extreme caution. Chlorpromazine is equally effective in the treatment of chronic regressed female psychotic patients and its toxic effects are much less serious. It seems to us that if either drug is to be used chlorpromazine is the drug of choice.

A reference to the pharmacology of phenothiazine itself shows that liver damage and jaundice, tachycardia, and sensitization of the skin to ultra-violet light are amongst the side-effects which brought it to be regarded as too toxic for use in humans (Martindale, 1952). It is clear that the derivatives of phenothiazine at present in use have toxic side-effects which are by no means negligible and which in some respects are similar to those of the parent substance. Further research is required in an effort to eliminate this unfortunate toxicity in drugs which otherwise seem to be valuable in mental hospital practice.

Summary and Conclusions

A controlled investigation into the effectiveness of "pacatal" in reducing the incidence of incontinence, noisiness, and aggression in chronically regressed psychotic female in-patients is described.

Pacatal was effective in reducing the number of noisy, aggressive, and incontinent acts in these patients, most of whom were suffering from schizophrenia.

Unfortunately, the high incidence of toxic side-effects in this group of patients suggests that the widespread use of pacatal is unjustifiable, at least until considerable evidence to the contrary is available. The toxicity of chlorpromazine, while not negligible, does not seem to be so serious, and it would appear to be the drug of choice. But where sensitivity to chlorpromazine has developed and where a drug of the phenothiazine type is strongly indicated, it would seem justifiable to use pacatal so long as close supervision of the white-blood-cell picture and of bowel and bladder function is maintained.

Acknowledgment is due to William R. Warner and Co. Ltd., who made supplies of pacatal freely available; to Dr. J. D. Silverston, medical superintendent of Lancaster Moor Hospital, for permission to perform the investigation; to Mr. H. Lewty, hospital pharmacist, for his assistance; and to the nursing staff, without whose help this investigation could never have been made.

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NICOTINYL ALCOHOL TARTRATE IN INTERMITTENT CLAUDICATION

BY

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The purpose of this investigation was to assess the value of nicotinyl alcohol tartrate ("ronicol") in the treatment of patients suffering from severe intermittent claudication secondary to generalized arteriosclerosis.

Nicotinyl alcohol tartrate is the alcohol corresponding to nicotinic acid, and has essentially the same vasodilator properties as the latter. However, its action is more sustained than that of nicotinic acid, probably because, in addition to the vasodilator properties of the alcohol itself, partial metabolism of it in the body results in the gradual release of nicotinic acid. The vasodilator effect of nicotinyl alcohol tartrate is mainly on the small arteries and arterioles. A number of investigators in the United States and in Europe have reported encouraging results with its use in the treatment of peripheral vascular disorders.[1-10] However, although the drug is widely used in Great Britain, no report has yet been published describing a controlled investigation of its use in intermittent claudication.

Plan of Present Trial

The investigation was carried out on the "blind" principle; the majority of the patients had previously been admitted to hospital for full investigation and all had been treated previously with other compounds alleged to be of value in intermittent claudication. For inclusion in the trial, patients had to fulfil the following criteria: *(a)* There had been present for at least two months a severe gripping pain lasting for more than one minute in one or other of the calf muscles, coming on after a constant amount of exercise and relieved by a few minutes' rest. *(b)* Pulsation was absent in one or other of the palpable arteries in the affected limbs. *(c)* The skin of the extremity was blue or gangrenous and distinctly colder than that of the less affected limb.

Patients were excluded from the series if they were suffering from any other serious disease, correction of which might have influenced the assessment of the results. Congestive heart failure, when present, was always corrected by appropriate treatment in hospital before the patient was included in the series.

Once the diagnosis had been established all treatment was withheld for a period, in order to prevent any "overlap" of therapeutic effects. Patients were then treated with either nicotinyl alcohol tartrate, one 25-mg. tablet four times daily, or with dummy tablets of identical appearance. Treatment was allotted by random selection by an independent person in the pharmaceutical department and I did not know the distribution of the patients until after the results of the trial had been assessed. The treated and control groups were comparable in respect of age and sex.

The series originally contained 50 patients, but by the end of the trial only 30 remained for final assessment. Of the remaining 20 patients, 15 died before the end of the trial, three moved to another area, and two refused to complete the course of treatment. It must be appreciated that, when organizing a trial using such poor clinical material over a fairly prolonged period, deaths from coronary thrombosis, cerebral haemorrhage, or renal complications, as a result of the generalized arteriosclerosis, are inevitable. All the case records of patients who died were studied, and it was decided to exclude them from the assessment of results because the duration of their treatment was too variable for useful assessment. The losses by death did not affect the comparability of the treated and control groups.