χ^2 comes to 9.6 for 2 degrees of freedom, which corresponds to a probability of under 1%. There is good evidence, therefore, that patient-drug interaction exists in this experiment—that is, that though in general tab. codein. co. is the better drug, for some people N.A.P.A.P. is consistently superior.

Discussion

We have thus reached the conclusion that, under the conditions of this experiment, tab. codein. co. in a dosage of two tablets three times a day is for most patients a significantly better analgesic than N.A.P.A.P. in a dosage of 1 g. three times a day. This ignores possible differences in side-reactions, which were inquired for every week. Only three patients complained of consistent side-effects—that is, during both weeks that the same drug was being taken. The complaint was of malaise in one and nausea in the other two, and occurred with tab. codein. co. Apart from these three cases the number of inconsistent side-effects was slightly greater during the administration of tab. codein. co. than with N.A.P.A.P. and consisted mainly of constipation, nausea, and giddiness, but no statistical significance between the two drugs in this respect could be demonstrated.

A significant minority of patients judged consistently that for them N.A.P.A.P. was the better drug. It is just possible that despite appearances some of these patients were able to detect a difference in some aspect of the tablets; if so, then the consistency of the second response might be spurious, suggestion being carried over from their first preference to sway their judgment on the second trial. But if we discount this possibility, as we think we may, it seems we have proof of the individual reaction to different types of analgesic.

Some patients took additional analgesics, mostly acetylsalicylic acid or tab. codein. co., during the whole or part of the trial period, but we can find no evidence that this tended to produce a preference for one drug rather than the other, or to produce consistency in preference rather than inconsistency. There was no evidence of preference for one or the other drug amongst patients belonging to any particular diagnosis group.

Lastly, a word should be said about the use of sequential analysis in a trial of this sort. We found this technique very useful and readily communicable to physicians without statistical sophistication: we hope this experiment will further its introduction into clinical trials, and direct attention also to the possibilities and desirability of including in the statistical design a test of patient-drug interaction, or patients' personal suitability for a particular drug.

Summary

N-acetyl-*p*-aminophenol (N.A.P.A.P.) is the non-toxic metabolite of acetanilide and phenacetin through which those drugs appear to exert their antipyretic and analgesic action in the human body, and has recently come on to the British market under the trade name of "panadol."

A controlled clinical trial of the analgesic effect of N.A.P.A.P. compared with that of tab. codein. co. *B.P.* has been carried out in patients suffering from chronic painful rheumatic conditions. Every patient received one drug for a period of a week followed by the other during a second week, and at the end of the fortnight was required to state which drug was the more effective. During the following fortnight a second similar comparison was made. The drugs were given under a randomization scheme which ensured that at no time did either the patient or the doctor know which drug was being taken.

The statistical method known as sequential analysis was used, the principles and advantages of which are described. In the main analysis only patients whose

preferences were consistent from one fortnight to the next were plotted. After 42 patients had been tested the analysis terminated with the result that tab. codein. co. 2 tablets three times a day was in general superior to N.A.P.A.P., 1 g. (2 tablets) three times a day. No significant side-effects were noted during the administration of N.A.P.A.P.

The repetition of the test in each patient makes it possible to assess patient-drug interaction—that is, whether there is a significant tendency for particular patients to prefer N.A.P.A.P. even though the majority prefer tab. codein. co. A χ^2 test between the numbers whose preferences were consistent and those who were inconsistent shows that this tendency does in fact exist.

Thus the design of the experiment permits us to state: (1) that tab. codein. co. is a superior analgesic to N.A.P.A.P. in the majority of patients of the sort we tested; and (2) that nevertheless a significant minority of individuals judge that for them N.A.P.A.P. is a better analgesic.

We wish to thank Bayer Products Ltd., who supplied the drugs; Dr. P. Bauwens for his advice and for permission to carry out the trial; Dr. R. P. Hickey for his assistance; and Dr. R. S. Stacey and Dr. P. Armitage for their criticism and advice during the preparation of this paper.

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BARBITURATE POISONING TREATED WITH AMIPHENAZOLE AND BEMEGRIDE

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Amiphenazole ("daptazole"; 2:4-diamino-5-phenylthiazole hydrochloride) and bemegride ("megimide"; β -ethyl- β -methylglutarimide) were introduced as a result of work by Shaw and Shulman (1955) and Shulman *et al.* (1955). Twelve cases of fairly severe barbiturate intoxication, in which all the patients were unconscious on admission, treated with these two drugs are recorded below.

Method

All the patients were first seen in the casualty department and admitted to the medical wards, where their condition was assessed and a full examination made, particular attention being paid to the depth of coma. This was followed by a stomach wash-out with a solution of dilute sodium bicarbonate, 4 oz. (114 ml.) of this solution remaining in the stomach after the wash-out had been completed. The airway was kept clear, using suction or intubation as necessary; and in all cases a laryngoscope was passed to determine whether laryngeal reflexes were present. A 5% glucose-saline intravenous drip was set up and continued running at a rate of 40 drops a minute throughout the treatment—that is, until the patient recovered consciousness. All patients were given 600,000 units of procaine penicillin at once and then twice daily for five days. Amiphenazole and bemegride were injected intravenously at a rate of 1 ml. of amiphenazole and 10 ml. of bemegride every three minutes until a level of light anaesthesia was attained. The strengths

of the solutions used were, 0.5% solution of bemegride (5 mg. per ml.), and a 1% solution of amiphenazole (10 mg. per ml.), the latter being made up immediately before use.

Postural drainage and breathing exercises were begun and continued daily throughout the patient's stay in hospital. Eleven of the cases regained full consciousness within 12 hours.

Case Reports

Case 1.—A married woman aged 58 was admitted to hospital in coma after taking 15 "carbrital" capsules. On examination she was unresponsive to any stimuli; B.P. 90/0; pulse 80, feeble and regular. Deep reflexes were absent except for plantars, which were flexor. The pupils reacted sluggishly to light and accommodation. She was treated with a total of 3 ml. of amiphenazole and 30 ml. of bemegride and regained full consciousness in 10 hours.

Case 2.—A married woman aged 51 was admitted in coma after taking 15 3-gr. (0.2-g.) tablets of amylobarbitone sodium. On examination she was unresponsive to any stimuli; cyanosed; B.P. 100/40; pulse 110, irregular and of poor volume; systolic murmur at the apex and aortic areas. Deep reflexes were absent except for plantars, which were flexor. The pupils were contracted and responded sluggishly to light and accommodation. She was treated with a total of 8 ml. of amiphenazole and 80 ml. of bemegride and regained full consciousness in nine hours.

Case 3.—A man aged 55 was admitted in coma after taking 15 3-gr. (0.2-g.) tablets of amylobarbitone sodium two and a half hours before admission. On examination he was unresponsive to any stimuli; B.P. 100/50; pulse 84 and regular. Deep reflexes were present but diminished; plantars flexor. The pupils were contracted and reacted sluggishly to light and accommodation. He was treated with a total of 18 ml. of amiphenazole and 180 ml. of bemegride and regained full consciousness in 11 hours.

Case 4.—A man aged 28 was admitted in coma after taking 12 carbrital capsules in mistake for mints in the cinema. On examination he was unconscious but responded to painful stimuli; B.P. 100/60; pulse 70. Deep reflexes were present but diminished; plantars flexor. The pupils were dilated and reacted sluggishly to light and accommodation. He was treated with a total of 4 ml. of amiphenazole and 40 ml. of bemegride and regained full consciousness in nine hours.

Case 5.—A married woman aged 36 was admitted in coma after taking 10 1-gr. (65-mg.) tablets of phenobarbitone one and a half hours before admission. On examination she was unconscious and unresponsive to any stimuli; B.P. 100/60; pulse 88 and regular. Deep reflexes were present but diminished. The pupils were contracted and reacted sluggishly to light and accommodation. She was treated with a total of 3 ml. of amiphenazole and 30 ml. of bemegride, became semi-conscious and muttered unintelligibly, and regained full consciousness in eight and a half hours.

Case 6.—A man aged 45 was admitted in coma after taking 15 tablets of butobarbitone one hour before admission. On examination he was unconscious and unresponsive to any stimuli; B.P. 90/60; pulse 68 and regular. Deep reflexes were present but diminished; plantars flexor. The pupils were dilated and did not react to light and accommodation. He was treated with a total of 4 ml. of amiphenazole and 40 ml. of bemegride and regained full consciousness in seven hours.

Case 7.—A man aged 49 was admitted in coma resulting from 20 1-gr. (65-mg.) tablets of phenobarbitone taken one hour before admission. On examination he was unconscious and unresponsive to any stimuli; B.P. 90/40; pulse 120 and feeble. Deep reflexes were present but diminished; plantars flexor. The pupils were contracted but reacted to light and accommodation. He was treated with a total of 5 ml. of amiphenazole and 50 ml. of bemegride and recovered full consciousness in nine hours.

Case 8.—This patient, the same as in Case 2, now aged 52 was admitted in coma after taking 25 3-gr. (0.2-g.) tablets

of amylobarbitone sodium one and a half hours before admission. On examination she was in coma and unresponsive to any stimuli; B.P. 90/40; pulse 100 and regular. Deep reflexes were absent; plantars flexor. The pupils were dilated and did not react to light and accommodation. She was treated with a total of 10 ml. of amiphenazole and 100 ml. of bemegride, became semi-conscious, and regained full consciousness in six hours.

Case 9.—A married woman aged 29 was admitted in coma after taking 8 3-gr. (0.2-g.) tablets of amylobarbitone sodium three hours before admission. On examination she was unconscious and unresponsive to any stimuli; B.P. 100/50; pulse 80. Deep reflexes were present but diminished. The pupils were dilated and did not react to light and accommodation. She was treated with a total of 9 ml. of amiphenazole and 90 ml. of bemegride and regained full consciousness in eight hours.

Case 10.—A married woman aged 34 was admitted in coma after taking 10 3-gr. (0.2-g.) tablets of amylobarbitone sodium and 20–25 25-mg. tablets of pethidine. On examination she was unconscious and unresponsive to any stimuli; B.P. 100/40; pulse 120 and feeble. Deep reflexes were absent in the lower limbs and diminished in the upper limbs; plantars extensor. The pupils were contracted and did not react to light and accommodation. She was treated with 100 mg. of nalorphine hydrobromide and a total of 4 ml. of amiphenazole and 40 ml. of bemegride, became semi-conscious, and regained full consciousness in three hours.

Case 11.—A single woman aged 25 was admitted in coma after taking 20 carbrital capsules and 20 3-gr. (0.2-g.) tablets of amylobarbitone sodium from seven to eight hours previous to admission. On examination she was unconscious, cyanosed, unresponsive to any stimuli; respirations were slow and stertorous; B.P. zero; pulse 130 and feeble. Deep reflexes were absent except for plantars, which were extensor. The pupils were dilated and did not react to light and accommodation. She was treated with 29 ml. of amiphenazole and 290 ml. of bemegride and became semi-conscious. She relapsed after one hour. A further 15 ml. of amiphenazole and 150 ml. of bemegride were given and full consciousness was regained 17 hours after admission.

Case 12.—A man aged 49 was admitted in coma after taking 30 1½-gr. (0.1-g.) tablets of phenobarbitone sodium two hours before admission. On examination he was unconscious and unresponsive to any stimuli; B.P. 100/60; pulse 100 and feeble. Deep reflexes were absent except for plantars, which were extensor. The pupils were contracted and did not react to light and accommodation. He was treated with a total of 22 ml. of amiphenazole and 220 ml. of bemegride and recovered full consciousness in 12 hours.

Comment

It is obviously difficult to compare these cases critically owing to the variety of barbiturates taken, the length of time of coma before the beginning of treatment; and the fact that it was not possible to estimate the blood barbiturate in any of them. However, several salient points do emerge from the small experience gained with this form of treatment: (1) A safe level of consciousness can be attained in a short period of time, which can be maintained and gradually improved to full consciousness in a matter of hours. (2) The incidence of chest infection is minimized. In these cases it was reduced to zero, and all the patients were able to look after themselves within 24 hours. (3) The stay of the patient in hospital was reduced, the time varying from five to nine days—an important factor, bearing in mind the high incidence of barbiturate intoxication and the shortage of beds in a ward for acute medical cases.

Summary

Twelve cases of fairly severe barbiturate poisoning were treated with amiphenazole and bemegride. All the patients regained consciousness within 24 hours, the

majority well within this period. No deaths occurred, and there was no incidence of chest infection in any of these cases. The stay of the patients in hospital was cut down dramatically compared with former methods of treatment. Although the number of cases treated is small, I feel that it is worth while reporting them, in view of the results obtained, which, in my opinion, are a vast improvement on the previous methods at our disposal.

I am indebted to Drs. W. A. Jaques, G. D. Owen, and A. W. B. Edmunds, consultant physicians at this hospital, for permission to publish these cases. In particular I must thank Dr. Edmunds for his advice, encouragement, and criticism, without which I should have been unable to present these cases.

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Medical Memoranda

Case of Strychnine Poisoning

Apart from accidental strychnine poisoning, particularly in young children, reports of attempted suicide with strychnine sulphate are uncommon. The toxic dose of strychnine in man appears to vary from about 2 mg., which has resulted in unpleasant symptoms, to about 15 mg., which has caused death. Recovery, however, has taken place after 1 g. or more has been ingested (Thienes and Haley, 1955).

The following case is of an intelligent boy aged 14 who obtained two $\frac{1}{4}$ -gr. (50-mg.) capsules of pure strychnine and swallowed them impulsively after a quarrel with his mother.

CASE REPORT

The boy was admitted to hospital about one and a half hours after 1½ gr. (100 mg.) of strychnine had been swallowed. He was fully conscious. Classical intermittent strychnine convulsions, occurring every few minutes, were present. He complained of severe pain, especially in his back, neck, and limbs. His colour was normal, and he looked extremely anxious. A mild stimulus such as holding his wrist produced a generalized contraction. He admitted he had swallowed the capsules of strychnine. No other physical examination was made at this stage because touching him caused convulsions.

He was immediately transferred to the theatre, where he was given atropine sulphate, 1/100 gr. (0.65 mg.) intravenously, followed by thiopentone sodium, 0.5 g., and suxamethonium chloride, 50 mg. A cuffed endotracheal tube, size 7, was passed and controlled respiration begun. The convulsions were then controlled by an intravenous infusion of 1 pint (570 ml.) of normal saline to which 1.5 g. of thiopentone sodium and 200 mg. of suxamethonium chloride had been added. The rate of drip was regulated to 20–30 drops a minute as required to maintain muscular relaxation. His blood pressure was 120/70 and pulse 120.

A wide-bore stomach tube was passed and a few ounces of fluid aspirated. This was followed by several wash-outs. The stomach contents were sent for analysis.

As a cover against respiratory infection penicillin was given intramuscularly and a catheter inserted into the bladder.

Still anaesthetized, the patient was taken to a single room. After six hours the anaesthetic was stopped for approximately two minutes, but tetanic contractions immediately developed. Rigidity of all muscles and marked ankle clonus were present. The thiopentone–suxamethonium drip was therefore continued for another six hours, then stopped again. No signs of contractions occurred, the limbs and

neck muscles remaining quite flaccid. Altogether 1 pint (570 ml.) of normal saline and 1½ pints (850 ml.) of glucose-saline, containing 3.25 g. of thiopentone and 500 mg. of suxamethonium, were given in 12 hours.

On stopping the anaesthetic 3 gr. (100 mg.) of phenobarbitone sodium was injected intramuscularly. The cuffed endotracheal tube was replaced after six hours by an ordinary tube, so as to prevent damage to the trachea by pressure.

The following day the boy merely complained of some back pain and a sore throat, otherwise he was quite well. He was discharged after a week's observation.

A large amount of strychnine was found in the gastric contents and the urine.

COMMENT

As in the treatment of tetanus so in this case of strychnine poisoning, complete control of the convulsions by an anaesthetist using a general anaesthetic plus a muscle relaxant is required.

It was of particular importance to aspirate the stomach after induction of anaesthesia, for a quantity of strychnine was found in the mucous gastric contents, although no food was recovered and ingestion of strychnine had taken place one and a half hours previously. The need for rapid treatment is shown.

It is of interest that in some cases of strychnine poisoning a reappearance of convulsions has been reported more than 48 hours after initial treatment. Strychnine is apparently again released into the blood stream by the liver. In the above case no further symptoms or signs of strychnine poisoning appeared.

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Acute Haemolytic Anaemia following Sulphadimidine Therapy

Acute haemolytic anaemia is now a recognized complication of medication with the sulphonamide group of drugs. It was first described by Harvey and Janeway (1937) during sulphanilamide therapy. Since then many further cases have been reported with sulphathiazole (Rothstein and Cohn, 1942), with sulphapyridine (Ravid and Chesner, 1940), and with sulphadiazine (Ross and Paegel, 1946). In addition, comprehensive reviews have been published by Wood (1938) and by Long *et al.* (1940).

No case, however, has yet been recorded of haemolytic anaemia following sulphadimidine ("sulphamezathine") therapy; indeed, toxic effects following the use of this drug are rare and usually limited to mild nausea and vomiting, and it is generally regarded as the "best sulphonamide for routine use" (*National Formulary*, 1955, p. 41).

CASE REPORT

A boy aged 2½ years was admitted to hospital on January 22, 1956. Five days previously he had developed acute otitis media preceded by 24 hours' diarrhoea, for which he had been given 1 g. of sulphadimidine, followed by 0.5 g. six-hourly to a total of 8 g. On January 20 he suddenly began passing dark urine and became progressively jaundiced.

On examination in hospital he was extremely jaundiced and obviously pale and still had diarrhoea, the fluid motions being dark brown in colour with no visible blood or mucus. There was tachycardia, the pulse rate was 160, and the temperature 99.4° F. (37.4° C.). The liver was enlarged to two fingerbreadths, but the spleen could not be felt. A history of measles in August, 1955, was subsequently revealed for which he had then received a short course of sulphadimidine to a total of 3 g.