social aspects of their patient's problem. But it is gratifying that in recent years there is an increasing awareness that the queries which epilepsy raises are not concerned solely with accurate diagnosis of the cause and with instituting the best treatment of the fits, but also with ensuring that the epileptic is given the fullest opportunities to take his place as a full and active member of the community in which he lives.

TREATMENT OF CERTAIN SIDE-EFFECTS OF MORPHINE

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The disadvantageous side-effects following the administration of morphine may be as follows: respiratory depression, nausea, vomiting, and central nervous system depression (narcosis).

Nalorphine (N-allylnormorphine) (Unna, 1943) has been introduced to overcome respiratory depression. There is also some evidence that succinic acid may be of benefit (Trautner, Trethewie, and Gershon, 1953). It will be shown below that amiphenazole ("daptazole") does not control the nausea and vomiting induced when morphine is given to healthy volunteers, although McKeogh and Shaw (1956) have found that scarcely any vomiting occurred when amiphenazole and morphine (in large doses) were given to 127 patients for the treatment of intractable pain in terminal carcinoma. The series has now been extended to about 400 cases over a period of three years. Holmes (1956) did not report any emesis when amiphenazole (15 mg.) and morphine (30 mg.) were administered during childbirth. A similar lack was described by Hügin (1956) when the two drugs were used to control post-operative pain. There is some evidence that the mental depression or narcosis induced by morphine is counteracted by amiphenazole (McKeogh and Shaw, 1956; Gershon, Bruce, and Shaw, unpublished).

It would thus appear that to control the side-effects of morphine completely three drugs are necessary—namely, N-allylnormorphine for respiratory depression, amiphenazole for narcosis, and a third for nausea and vomiting.

In another paper (Gershon and Shaw, 1958) it has been suggested that some of these side-actions may be due to the release of histamine by morphine. Other toxic effects which may have a similar origin are giddiness, headache, and pruritus.

It is the purpose of this paper to show that the incidence of vomiting following the use of morphine is higher and more severe than is generally thought and that this distressing symptom can be controlled by cyclizine hydrochloride ("marzine"). Definite evidence is

presented to show that amiphenazole counteracts the central nervous system depressive action of morphine. The psychological part of this work has been carried out by D. W. Bruce.

Clinical Material

The conclusions to be drawn from this investigation are based on three separate experimental series and some special case histories, the work being designed so that the major therapeutic exhibitions of morphine would be covered—namely: (a) Sufferers from incurable painful diseases, where some degree of habituation is soon established and the incidence and severity of side-effects fall off. (b) Pre- and post-operative patients. This group is not a homogeneous one, but comprises a wide range in respect of age and physical conditions. The group, especially the post-operative section, is a particularly important one, as nausea, dry retching, and vomiting can cause serious surgical sequelae. The complications may range from simple interference with wound union to lesions and extension thereof, and also may be an important factor in the production of haematomas in the region of the wound, with resultant secondary infection. (c) The third major use of morphine is as an emergency analgesic for accident casualties and war-wounded, and where relatively high doses are required.

It therefore seemed desirable at the outset to establish the incidence and severity of the side-effects of doses of the order of 15–30 mg. Morphine was given by injection throughout the tests, usually intramuscularly but occasionally intravenously.

First Series: Trial on Army Volunteers

Forty-six volunteers were available. On the first day a test dose of morphine, 1/6 gr. (10 mg.), was injected. Three subjects were considered unduly sensitive because of nausea, light-headedness, or drowsiness, and were excluded from the main tests. Another volunteer was discharged because of the onset of an asthmatic attack some hours after the test dose. Clinically it was slight, but it was thought better not to proceed with this person.

The remainder were divided at random into six groups of seven men. Five schedules of medication were used throughout: (1) morphine, 30 mg., and cyclizine, 50 mg.; (2) morphine, 30 mg., cyclizine, 50 mg., and amiphenazole, 40 mg.; (3) cyclizine, 50 mg.; (4) amiphenazole, 40 mg.; (5) distilled water, 1 ml. Each group of volunteers received each of these schedules once, and the rotation was such that no group received morphine on two consecutive days. All subjects had three injections of morphine over a six-day period, in addition to the initial test dose of 10 mg. (6) This schedule consisted of morphine, 30 mg., on one occasion; morphine, 20 mg., on two occasions; morphine, 20 mg., and amiphenazole, 40 mg., on two occasions.

An anaesthetist was in attendance with the necessary resuscitative apparatus, but his services were not needed.

An analysis of the reaction to the five-dosage schemes which included morphine is presented in Table I. Amiphenazole alone produced negligible symptoms. Some soreness of the arm lasting up to two hours was observed by 40% of subjects, and 20% mentioned a slight degree of drowsiness. A similar degree of drowsiness was noticed in the controls (distilled water). With cyclizine alone 40% of the subjects noticed drowsiness and 10% experienced slight headache.

Effects of Morphine

It would have been experimentally desirable to submit a larger number to morphine (30 mg.), but after the first day's experiences repetition of the experiment on other groups was not considered morally justifiable. As the degree of illness and vomiting experienced was more than the

volunteers could ethically be asked to bear, comparison of the performances of this group when on the other schedules with the performances of other groups does not suggest that those receiving morphine alone were other than average in their reactions.

Care was taken to apply the criteria regarding morphine alone, included in Table I, as uniformly as possible. The two observers worked independently to a large extent, and found that their results were in close agreement. It is unlikely that any significant degree of tolerance was established over the period of the experiment.

Dizziness and ataxia were usually early symptoms of morphine administration, whereas drowsiness was usually delayed some two or three hours, by which time the earlier symptoms were much reduced. Vomiting was sometimes early but usually delayed, sometimes occurring up to seven hours after the injection. Itch, tremor, and spasm of the urinary sphincter were experienced early, and were persistent. Itch commonly involved the nose and face, but could occur in any part of the body. It was sometimes severe, and one subject complained that he felt that he was being attacked by a bag of fleas. There was a striking lack of correlation of the severity of reaction to body weight.

Hospital admission was not on any occasion due to serious illness, but rather to the inadvisability of the subjects returning to their lines overnight owing to persistent nausea or vomiting, headache, drowsiness, prolonged weakness and pallor, or shakiness.

Reactions which were severe enough to necessitate recumbency early in the test usually persisted, sometimes up to ten hours. Subjects of such reactions constituted the main proportion of hospital admissions. When severe symptoms were delayed for two to four hours the subject might be compelled to lie down for periods varying from ten minutes to two hours. Persistence beyond this length of time was unusual.

In view of hospital experience it is surprising that the incidence of incapacity in healthy young men after an injection of 30 mg. of morphine should prove so high. If such reactions occur among battle casualties they must add considerably to the patient's distress and to the apparent severity of his clinical condition.

Effects of Other Substances

Amiphenazole.—Table I shows that amiphenazole produces a considerable reduction of sleepiness, and small reduction of nausea and vomiting in acute morphine administration. The drug did not produce results comparable with those recorded in chronic morphine administration to sufferers from incurable painful diseases, in which circumstances it appears to enhance alertness and well-being to a major degree (McKeogh and Shaw, 1956) (see also Second Series and Special Cases).

TABLE I.—Incidence of Undesirable Morphine Effects After the Five Main Dosage Schedules; Expressed as Percentages, Usually to the Nearest 5%

Symptoms and Signs	Morphine, $\frac{1}{2}$ gr. (30 mg.) (8 Subjects)	Morphine, $\frac{1}{2}$ gr. (20 mg.) (17 Subjects)	Morphine, $\frac{1}{2}$ gr. (20 mg.), Amiphenazole, 40 mg. (19 Subjects)	Morphine, $\frac{1}{2}$ gr. (30 mg.), Cyclizine, 50 mg., Amiphenazole, 40 mg. (42 Subjects)	Morphine $\frac{1}{2}$ gr. (30 mg.), Cyclizine, 50 mg. (40 Subjects)
Nausea ..	100	65	40	75	42
Vomiting ..	62	35	20	50	25
"Ataxia" ..	100	80	—	—	—
Dizziness ..	100	50	65	90	90
Sleepiness ..	100	80	45	85	95
Tremor ..	100	35	10	70	70
Itch ..	75	65	65	85	85
Difficulty in micturition	75	35	35	38	50
Reactions requiring recumbency at some period	100	35	25	65	40
Admission to hospital ..	62	30	10	33	17

Cyclizine Hydrochloride.—Table I shows that significant and useful suppression of the undesirable side-effects of 30 mg. of morphine was obtained by oral administration of 50 mg. of cyclizine hydrochloride a few minutes before the injection. The reduction of nausea, of vomiting, and of the severity of shakiness were the main reasons responsible for the decrease of recumbency during the test and of hospital admission overnight. It is possible that injection of this agent would have produced even better results, as absorption must have been slow in an appreciable proportion of cases (see Special Cases).

Cyclizine and Amiphenazole in Combination.—Table I shows that, although amiphenazole alone produces a slight improvement and cyclizine alone a considerable reduction of morphine toxicity, the combination of both is less effective than cyclizine alone.

The three volunteers excluded from the main experiment after the test dose of morphine, 10 mg., were given all combinations of drugs at a level of morphine 15 mg., but no conclusive difference in response with any combination was demonstrable.

A subclinical degree of "ataxia" was observed by almost all subjects given morphine (in combination with the other drugs). They stated that some degree of concentration, or of conscious effort, was required to perform voluntary movements with precision. Even after 30 mg. of morphine alone "ataxia" was not severe enough to be clinically obvious, and could be controlled by the subject, provided that other symptoms, such as nausea, vomiting, or faintness, did not prevent the necessary effort. The incidence of this symptom was not materially reduced by either cyclizine or amiphenazole, or both in combination.

To summarize, amiphenazole was found to produce slight improvement, and cyclizine considerable improvement, in the incidence of undesirable reactions. Amiphenazole exerted its chief beneficial effect in counteracting the drowsiness and sleepiness.

A combination of both cyclizine and amiphenazole was less effective in the control of these reactions than cyclizine alone, possibly because of the drowsiness produced by cyclizine alone. It might be mentioned that the drowsiness produced by cyclizine was not marked. Much of the drowsiness could be accounted for by boredom and the humid conditions of the room in which the men were confined.

Results Obtained with Performance Tests

The subjects in this trial all underwent two psychological performance tests—namely, the Australia Council of Educational Research (A.C.E.R.) Speed and Accuracy Test and the Minnesota Rate of Manipulation Test (Formboard Test) (1947), in order to ascertain the effects of the drugs on their performance as measured by these tests. The A.C.E.R. test (Table II) used was the standardized form with two-part number-checking and name-checking, six minutes being allowed for each section.

The Formboard test score (Table III) is the time in seconds taken to place blocks into the holes in the formboard.

Analysis.—As there is no technique at present available for dealing with missing values after a treatment has been omitted in experimental designs like the one employed, the following method was used for each section. The mean of all results for the group of people on the same treatment on the same day was used instead of seven individual values and the experiment was analysed by the method of Yates (1936).

From these results it may be concluded that (1) water, cyclizine, and amiphenazole have indistinguishable effects. The mean score for all three is 135.9; (2) the means of both

TABLE II.—Mean Scores for Treatments (A.C.E.R.)

Water	Cyclizine	Amiphenazole	Morphine + Cyclizine	Morphine + Cyclizine + Amiphenazole
133	139	136	129.3	121.8

Difference required for significance between two means = 7.63, $P = 95\%$.

of the treatments morphine + cyclizine and morphine + cyclizine+amiphenazole are almost significantly lower than the above mean; and (3) the mean of morphine+cyclizine+amiphenazole is 7.50 less than that of morphine+cyclizine; the difference required for significance is 7.63 units, and thus the difference borders on significance.

TABLE III.—Formboard Test. Mean Scores for Treatments

Water	Cyclizine	Amiphenazole	Morphine + Cyclizine	Morphine + Cyclizine + Amiphenazole
234.8	239.4	241.6	244.95	252.45

Difference between two means for significance = 10.25, $P = 95\%$.

From these results it may be concluded that, (1) water, cyclizine, and amiphenazole are indistinguishable; (2) the mean score for morphine + cyclizine is not significantly greater than that of cyclizine or of amiphenazole; it is almost significantly greater than that of water; and (3) the mean score for morphine + cyclizine + amiphenazole is significantly greater than for any of water, cyclizine, or amiphenazole, but not for morphine + cyclizine.

Conclusions from Both Tests.—(i) Cyclizine and amiphenazole have no effect on performance as tested by either method. (ii) With morphine + cyclizine some depression of performance takes place. (iii) This depression is worsened by the inclusion of amiphenazole.

Second Series : Female Patients Awaiting Minor Surgery

Patients in good physical condition and without pain who were in hospital for some minor surgical procedure were given morphine, 20 mg., atropine, 0.7 mg., and amiphenazole, 25 mg., intramuscularly the evening before operation. The same schedule was repeated pre-operatively next morning but without amiphenazole. However, the observations that could be made after the morning pre-medication without amiphenazole were very limited, as the time of observation after injection was short, since the patients underwent operation usually within one to one and a half hours. This particularly affected the incidence of vomiting in this group, as vomiting was found to occur in the other group in the majority of the cases from two to nine hours after the injection. Thus the figures for vomiting (and nausea) are virtually valueless. The results are given in Table IV.

TABLE IV

Itchiness	Nausea	Vomiting	Sedation	Dizziness	Totals
With Amiphenazole					
5	18	14	8	12	34
14%	53%	44%	23%	30%	
Without Amiphenazole					
3	7	1	14	9	24
12%	26%	4%*	58%*	37%	

* Significant difference.

These results indicate that the incidence of side-effects after morphine in this group of patients is high, especially the unusually high incidence of nausea and vomiting. Furthermore, these symptoms were not affected favourably by the administration of amiphenazole. On the other hand, amiphenazole greatly reduced the degree of sedation (narco-sis) experienced with the morphine.

Third Series : Male Volunteers

In this trial a group of 28 students were given the following drugs: saline; morphine, 16 mg.; morphine, 16 mg., plus amiphenazole, 25 mg.; and morphine, 16 mg., plus cyclizine, 50 mg., plus amiphenazole, 25 mg. The drugs were administered intramuscularly with the exception of the cyclizine, which was given by mouth. They were then subjected to both the psychological tests (A.C.E.R. and Formboard) as reported above.

The incidence of undesirable effects in the various groups is shown briefly in Table V.

TABLE V

Drug	No. of Subjects	Nausea		Vomiting		Sedation		Dizziness	
		No.	%	No.	%	No.	%	No.	%
Morphine	7	4	57	3	43	3	43	1	14
Morphine + amiphenazole	7	3	43	3	43	1	14	1	14
Morphine + amiphenazole + cyclizine	18	2	11*	2	11	12	66	11	61*
Saline	28	1	4*	0	0*	1	4*	2	7

* Statistically significantly different from the morphine alone group.

A detailed statistical analysis of the results obtained with the A.C.E.R. and Formboard tests enabled the following conclusions to be drawn: Morphine and morphine + amiphenazole depressed performance, but the differences between the control and the test series were not statistically significant. When cyclizine was added to the morphine + amiphenazole, the performance was the same as the control in the case of the A.C.E.R. test and significantly better in the case of the Formboard test.

Special Cases

The types of clinical material available here were mainly cases of carcinoma, many of which were terminal cases. Some of these cases had been receiving morphine for relief of pain, but the incidence of side-effects in this population was low, about 1%. The results of the addition of amiphenazole as regards other effects have been fully recorded by McKeogh and Shaw (1956). It was found in this series that the addition of amiphenazole did not to any great extent decrease the already low incidence of the side-effects of morphine, such as nausea or vomiting.

Effect of Cyclizine on Morphine-induced Vomiting

Several trials were carried out with intravenous cyclizine to determine its efficacy in controlling the side-effects of morphine.

Case 1.—Mr. H. G., aged 34, had carcinoma of the rectum with secondaries in both lungs. He was found to be sensitive to morphine 15 mg. (with or without amiphenazole), methadone hydrochloride, 10 mg., and pethidine, 50 mg., each of these causing vomiting and dry retching. After a meal he was given an intravenous injection of 50 mg. of cyclizine, followed three minutes later by the intravenous injection of 15 mg. of morphine. He became a little drowsy, but obtained complete relief from pain, with the complete absence of any unpleasant side-effects such as nausea or vomiting. He was maintained on these drugs, given four times a day, until he died 10 days later. No vomiting ensued. On two occasions the cyclizine was given intramuscularly, but vomiting occurred. In other cases it was found that the cyclizine must be given intravenously, but this is not usual.

Case 2.—Mrs. R. V. had nausea and vomiting after each injection of morphine in hospital. Cyclizine, 50 mg. intramuscularly, included with each injection of morphine, gave full control of these side-effects over a period of three weeks with up to 10 mg. of morphine four times a day.

Case 3.—Miss V. B. gave a history of sensitiveness to morphine in that it always produced giddiness, nausea, and vomiting. Cyclizine, 50 mg., was given with each injection of morphine, with complete relief. She required only one injection of morphine in 20 hours to control pain, but on one occasion morphine and cyclizine were given at 6 p.m., and at 12 midnight morphine was repeated without cyclizine because of pain, and she vomited about seven hours later. She has since received cyclizine and morphine regularly twice daily for three weeks, with full control of side-effects.

Case 4.—Mr. R. W. had a history of intolerance to morphine, which caused nausea, vomiting, and giddiness. He was given morphine, 16 mg., and cyclizine, 50 mg., six-hourly, and this brought all unpleasant symptoms under complete control. After several days the dose of cyclizine was reduced to three times a day whilst the same dose of morphine was continued. He then vomited on several occasions, and when the cyclizine was restored to four times a day full control of side-effects was again established.

In the four other cases (Nos. 5, 6, 7, and 8) in this series similar results were obtained.

TABLE VI

Name	Age	Dose Morphine (mg.)	Effect	Cyclizine (mg.)	Immediate Effect	Delayed Effect
A. J. M.	69	30	Little drowsy; slight respiratory depression	50	Little more alert and mild temporary increase in respiration rate	Very drowsy. B.P. and respiration maintained
S. L. S. . .	55	130	" " "	100	" " "	No change
R. M. . .	65	165	" " "	100	" " "	Became little drowsy. Otherwise condition satisfactory
M. B. . .	62	65	" " "	100	" " "	Drowsy; confused, completely disorientated, restless, and disturbed. No improvement in respiration
M. W. . .	52	65	Drowsy; respiration markedly depressed	150	" " "	Drowsy—stuporous. Resp. rate depressed again. B.P. maintained at normal level. Became very stuporous, with vacant expression, glazed look, unable to answer questions, and mentally and physically retarded. Appears to have visual hallucinations. Returned to normal in 24 hours
E. K. . .	60	65	" " "	100	" " "	Very drowsy, appeared to be hallucinated for short time; confused, with incoherent mutterings
P. C. . .	61	100	Sleepy; respiration rate fell from 24 to 4 min.	75	" " "	Appears hallucinated; groping in air and grasping at bedclothes. Grossly disorientated, restless, and confused
R. M. . .	58	65	Sleepy	100	No change	Very drowsy and disorientated
F. W. . .	54	65	" Felt nausea	100	Feeling of nausea eliminated	Sleepy and progressively more drowsy. Resp. unchanged. B.P. maintained at normal level

Another group of patients were given varying doses of morphine (30–90 mg. intravenously) in order to produce a mild state of drowsiness with a degree of respiratory depression, and cyclizine was then injected intravenously to assess its effect on the condition produced (Table VI). The results and those of the cases above show that cyclizine is effective in controlling some of the side-effects produced by morphine (and pethidine), such as nausea and vomiting. However, it did not improve the level of consciousness in those subjects who were sleepy or drowsy after morphine—in fact, all these patients became more drowsy and more deeply narcotized. In some cases undesirable psychotic effects were produced by cyclizine. No improvement in respiration was produced by cyclizine in any case. It is of interest to note that, in spite of the sedative and depressant effects of cyclizine, the blood pressure in these patients was improved, or at least maintained.

Effect of Amiphenazale in Controlling Morphine-induced Narcosis

It may be that morphine and amiphenazale, given together for an extended period, bring about control of the various side-effects, which is not obtained in the acute experiments, in particular the action on C.N.S. depression. An illustration of such a result may be seen in the following cases.

Case 9

Mrs. E. S. had been on morphine, 105 mg. six-hourly, with amiphenazale, 120 mg. a day, for several months, and was kept in good physical and mental condition. She was first submitted to psychological testing during this phase, the Wechsler Memory Scale Form I (Wechsler, 1945) being used. On March 15, 1957, amiphenazale was suspended, and she was retested five days later, using the Form II Scale; no appreciable change in score was obtained. She continued in the same state for a period of two and a half weeks without amiphenazale.

On April 3 the patient complained of giddiness and felt "generally terrible." She was confused, depressed, and lacrimose, and her speech was unintelligible. She drowsed at intervals, and was vague and rambling. Morphine was continued and her condition remained much the same; psychological testing was carried out on April 4 at 2.30 p.m.

During the initial conversation and explanation of the test she was apparently normal (except for feelings of nausea and a slight tremor) and pleasantly co-operative as usual. She remembered personal details quite well. She became vague when asked the year, month, and day, and gave wrong answers. This may have been due to lack of concentration—at this stage she began to stare into space for short

periods. She could not repeat the alphabet—saying only about six assorted letters—and was then apparently under the impression that she had said it all correctly. Asked to count backwards from 20 to 1, she said "20, 17, April, May . . ." and then lapsed into incoherence. Asked to count "by fours," she just repeated "four" and returned for a moment to trying to count backwards.

Test result showed over 50% deterioration on the previous score. She was then restarted on amiphenazale, initially intravenously and orally, and then orally only. She began to improve after two days and was restored to her previous condition after four days, and test performance as tested on the sixth day was at the initial level.

During the next four months she was maintained on morphine and amiphenazale without the appearance of a similar episode. Her normal performance on psychological testing was maintained. At the end of this period, following palliative treatment, she became pain-free. The morphine was then withdrawn over a period of 10 days. Amiphenazale was maintained during this period and then discontinued. There were no withdrawal symptoms at any time. She was now retested by the Wechsler test, the score being the same as when she was receiving 420 mg. of morphine and 120 mg. of amiphenazale daily.

Comment.—It is of course possible that the patient had a transient cerebral vascular episode, when the amiphenazale was first withdrawn, but neurological examination did not support this. In any case the episode was not repeated during the next ten months.

Case 10

Mr. A. W. had been on morphine, 45 mg. six-hourly, for several weeks and had become progressively more drowsy. In addition he became more depressed, irritable, complaining, and inhibited. On July 2, 1957, it was intended to submit him to psychological testing. He was very drowsy and had to be roused. He began to complain bitterly, and verged on tears about his incontinence, saying, "This only happens to babies." He seemed to be in great pain when he tried to make any movement. He continued talking in a very depressed way to the effect that there should be something to ease his pain, indicated how thin he was, and said he should be allowed or made to walk. He was completely untestable. On this date amiphenazale was added in a dose of 160 mg. daily, and after three days he was much brighter and looked and behaved in a more cheerful manner. On July 9 psychological testing could be carried out; he was happy to co-operate, and could understand the instructions and readily cope with the test situation. There was evidence of deterioration characteristic of senile change, in

keeping with his age (75) and condition. He was still somewhat confused, but there was a distinct improvement in his mood. He was now no longer depressed and was brighter and even aggressively self-confident.

Comment.—This antidepressant effect has often been observed clinically on this type of patient, two of which have been observed as closely as Case 10. This effect of amiphenazone has been mentioned by Hügin (1956) and McKeogh and Shaw (1956), and it is intended to investigate it by further psychological testing procedures (Gershon, Bruce, and Shaw, unpublished).

Case 11

Mr. R. W., aged 50, weight 112 lb. (50.8 kg.), had five months previously developed an ulcer on his right cheek which was skin-grafted. Four months later swelling of the graft occurred which broke down and discharged. A biopsy of the ulcer showed it to be sarcoma. Morphine and amiphenazone were administered as shown in Table VII in order

TABLE VII.—Details of Case 11

Date	Time	Morphine (mg.)	Amiphenazone (mg.)	Respirations	Condition
24/5/56	6, 7, 11 p.m.	10	20	24 (depth normal)	Awake
25/5/56	12 "	22	20	22	Sleeping
	6, 7, 11 a.m.	44	40	18	Awake
	12, 5 p.m.	65	40	14	"
26/5/56	6, 11 "	87	20	12	"
	12 "	98	20	11	Sleeping
	3 a.m.	98	20	14	"
	6, 7 "	110	40	14	Awake
27/5/56	12, 2, 5 p.m.	130	40	12	"
	6, 10 "	130	40	12	Drowsy
	1, 2, 4 a.m.	130	60	12 deep	Sleeping
	6 "	130	40	8 "	Awake

Grand total of morphine in 84 hours = 2,074 mg.

to control the pain. At no time was he in danger of respiratory failure. After May 27 he was maintained on morphine, 50 mg., and amiphenazone, 40 mg., four times a day, for eight weeks.

Discussion

In a previous paper (Gershon and Shaw, 1958) it has been shown, in animals, that a large element of the pharmacology of morphine is concerned with the histamine-like actions of morphine or the release of histamine by this drug. In short it was shown that a large number of antihistaminics would abolish a deep morphine narcosis and restore to a remarkable degree the normal conscious level of the animal.

The restoration is, however, not as marked as that obtained with amiphenazone. This applies especially to the tone of the limb muscles. After amiphenazone the morphinized animal walks or even runs; this is rarely seen after cyclizine (or any other antihistaminic). (For further references to work on histamine release by morphine see Robson and Keele, 1956).

In this paper it has been shown that the only really effective drug to control morphine-induced emesis is a mild antihistaminic, cyclizine chloride. On the other hand, the narcotic (sedative) action of morphine is best controlled by amiphenazone. These two results, in man, parallel the results obtained in animals.

There is also some evidence that amiphenazone can aid in the relief of morphine addiction (Ballantine, 1957). Two similar cases have been brought to our notice (see also Case 9).

Nalorphine (N-allylnormorphine) ("nalline," "lethi-drone") would appear to be the drug of choice to restore a morphine-depressed respiratory centre, although amiphenazone has some action in this regard.

It would appear that morphine, in healthy people, is not the dangerous drug that has hitherto been believed. In the present work 32 mg. of morphine has been given to 42 volunteers and 20 mg. to another group of 54 persons, none of whom had received morphine before. In no case was

there the slightest concern for the welfare of these patients on the grounds of respiratory depression. It would appear, however, that certain patients are susceptible to morphine. Thus in the first series 6 out of 48 volunteers were sensitive in various ways to 10 mg. of morphine. But even in this group respiratory depression was not the major concern. It is therefore advisable to ascertain this sensitivity by giving the conventional dose of 10–15 mg. If this amount is without untoward effect then the dose of morphine should be rapidly increased to 30 mg. or more until the patient receives complete analgesia lasting for, say, six to eight hours. A view that larger doses of morphine may be given more rapidly, yet with safety, has been expressed by Fraser, Isbell, and Van Horn (personal communication, 1957). These workers were able to give 500 mg. within a matter of ten days. According to them amiphenazone had no effect in aiding the attainment of this huge morphine dosage. Large as this dose is, it is not as great as that mentioned in Case 11 above, in which 826 mg. was given within 54 hours, a result which was obtained with amiphenazone. We did not feel ethically justified in repeating the experiment without amiphenazone.

In cases of severe pain, nausea and vomiting will be rarely experienced, but if these symptoms do occur they can be almost completely controlled by cyclizine. Oral cyclizine is usually effective in this respect. If this route of administration should fail the drug should be given by intramuscular injection. In several cases, especially Nos. 1 and 4, it was sometimes necessary to give the cyclizine intravenously to obtain complete control of the emesis.

If the large doses of morphine should produce undue sedation or central nervous system depression, this can be counteracted with amiphenazone. The objective assessment of the beneficial effect of amiphenazone on the mental depression produced by morphine is difficult to make. At present we are endeavouring to achieve this end with the aid of certain psychological tests. These results will be published later (Gershon, Bruce, and Shaw). Overton (1957) has described a case in exactly the same manner as had McKeogh and Shaw (1956), with respect to the mental outlook of a hopeless case of intractable pain in an advanced lymphosarcoma treated with up to 140 mg. of morphine (q.d.s.) and amiphenazone. Similar favourable results have been published by Dundee (1957). It will be seen from the histories of Cases 8 and 9 that the use of amiphenazone is essential in the long-term treatment of intractable pain with morphine. These results confirm the previous results of McKeogh and Shaw (1956).

Further evidence of the antidepressive effects of amiphenazone is provided by the observation that it has sometimes been necessary to discontinue the use of amiphenazone as death approaches. Some of the patients in the terminal stage have too much insight into their condition, and it is felt that it is more humane to let such patients die in a comatose condition. Similar ideas have been expressed to us by Dr. Ian Rae (personal communication). More recently dogs have been given morphine and amiphenazone for several weeks and then the amiphenazone has been withdrawn. The animals, which had previously been alert while on the mixture, became drowsy when the amiphenazone was discontinued (Shaw and Alexander). The benefits to be derived from the use of 30 mg. of morphine with 25–50 mg. of amiphenazone, post-operatively (especially after thoracic surgery), are described by Hügin (1956).

In cases of morphine-overdosage in man there is often an accompanying fall in blood pressure. Therefore it is interesting to note that when cyclizine was given intravenously to our patients after the administration of large doses of morphine (up to 100 mg.) there was a rise in blood pressure in every case.

Previous work (McKeogh and Shaw, 1956) has shown that amiphenazone is a safe and harmless drug; the same may be said of cyclizine when it is given orally. When administered parenterally, however (in the presence of morphine), there is little effect with doses of 50 mg., but larger doses produce

a drowsiness in the patients, and later in some cases there resulted confusion, disorientation, and hallucinations. These psychotic disturbances were, however, temporary, and may be due to anoxia.

In conclusion, then, one may say that the full control of the side-actions of morphine requires the use of three different drugs. N-allylnormorphine (nalorphine) for the control of respiratory depression, although this can be achieved only with the loss of analgesia. Amiphenazole combats central depression and its use is essential for the long-term treatment of intractable pain with large doses of morphine. Experience has shown that very often these large doses of morphine of the order of 600 mg. a day are required to keep the patient completely free of pain. Such treatment has been shown to be absolutely without danger in a series of over 400 cases. Larger doses of amiphenazole (40–100 mg., q.d.s.) than hitherto are now employed. Our wide experience places this drug as one of the safest in medicine. Cyclizine is the drug of choice for the control of vomiting or nausea. This drug is also completely harmless and there is no reason why a patient who experiences even the slightest degree of nausea from morphine (or pethidine) should not be spared the discomfort by a simple and safe treatment, oral medication usually sufficing, although occasionally the intramuscular or intravenous route must be employed.

Summary

Doses of morphine of up to 30 mg. have been given to volunteers and the effects noted. The most frequent side-effect is not respiratory depression but nausea and vomiting, the incidence of which may be as high as 30%. The onset of emesis may be delayed for seven hours. Other side-effects are described.

The nausea and vomiting may be completely controlled by the use of cyclizine chloride.

The central nervous system depression (narcosis) may be controlled with amiphenazole.

Provided the sensitivity of the patient to small doses is first ascertained morphine is not a dangerous drug. All the side-actions can now be controlled.

Large doses of morphine (up to 200 mg., q.d.s.) may be required to control chronic pain. The patient should not be denied the benefit of complete analgesia on the score of side-actions or addiction. The results of over 400 cases show such fears to be groundless when the appropriate antagonist is employed to control the particular side-action experienced by the patient.

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REFERENCES

- Ballantine, I. D. (1957). *Lancet*, 1, 251.
 Dundee, J. W. (1957). *Ibid.*, 1, 376.
 Gershon, S., and Shaw, F. H. (1958). *J. Pharm. (Lond.)*, 10, 22.
 Holmes, J. M. (1956). *Lancet*, 2, 765.
 Hügin, W. (1946). *Schweiz. med. Wschr.*, 86, 1100.
 McKeough, J., and Shaw, F. H. (1956). *Brit. med. J.*, 1, 142.
 Overton, F. C. (1957). *Nursing Mirror*, 104, March 29, p. XIII.
 Robson, J. M., and Keele, C. A. (1956). *Recent Advances in Pharmacology*, 2nd ed., p. 103. Churchill, London.
 Shaw, F. H., and Alexander, I. S. In preparation.
 Trautner, E. M., Trethnew, E. R., and Gershon, S. (1953). *Med. J. Aust.*, 2, 848.
 Unna, K. (1943). *J. Pharmacol. exp. Ther.*, 79, 27.
 Wechsler, D. (1945). *J. Psychol.*, 19, 87.
 Yates, F. (1936). *J. agric. Sci.*, 26, 301.

INFLUENCE OF INITIAL VACUUM ON STEAM STERILIZATION OF DRESSINGS*

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It is generally accepted that, in the sterilization of surgical dressings by steam under pressure, air must be efficiently removed from the sterilizer and its contents before steam is admitted. But opinions are divided over the best method of removing air. Most hospital sterilizers are fitted with steam ejectors which draw a preliminary vacuum of 10 in. (25 cm.) Hg or rarely up to 20 in. (50 cm.) Hg but do not reach anything like a vacuum of 29.92 in. (75.97 cm.) Hg which is required for complete removal of air. Perkins (1956) points out the dangers of relying on partial removal of air. He recommends that, instead of drawing a preliminary vacuum, air should be continuously removed by downward displacement through the use of thermostatic valves, ensuring the automatic control of air and condensate discharge. Recently it has been claimed that the most reliable method is to use a pump capable of rapidly producing a vacuum of at least 27–28 in. (68.5–71 cm.) Hg as in some modern German sterilizers (see Bowie, 1957).

Alder and Gillespie (1957) have pointed out that there is remarkably little precise evidence to support the statements that have been made about the merits of different ways of removing air. They measured residual air trapped inside dressings and found that double evacuation by means of a steam ejector up to about 20 in. (50 cm.) Hg gave rather more efficient removal of air than downward displacement, but neither of the methods they used could be relied upon to remove air completely, especially when drums were incorrectly loaded.

All those who have studied this problem, whichever method of air removal they recommend, agree that the effect of residual air is to delay the penetration of steam into dressings and so render the attainment of sterilizing temperatures slow and unreliable (Savage, 1937). The time taken to reach an arbitrary sterilizing temperature inside a standard surgical pack can therefore be used as an indicator of the efficiency with which air has been removed before the admission of steam. We have therefore investigated the influence of different levels of preliminary vacuum on the time taken to reach an arbitrary sterilizing temperature in surgical packs deliberately overloaded and badly sited in the sterilizer.

Materials and Methods

A horizontal jacketed autoclave of approximately 11 cu. ft. (0.31 cubic metre) capacity was used (Fig. 1). The steam was supplied at 46 lb./sq. in. (3.23 kg./sq. cm.) after having passed two separators. It was fed to the chamber and jacket independently after passing valves to reduce pressure to

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