and capillary congestion and endothelial swelling in the glomeruli of the kidney.

Discussion

Choubladze *et al.* (1956) have observed that a "large percentage" of patients with multiple sclerosis had antibody to E.H.A. virus. This, in conjunction with other virological studies of E.H.A. virus, led them to believe that there was infection with this virus in some cases of multiple sclerosis. They accordingly used a formalized preparation of E.H.A. virus called the "vaccine of Margoulis and Choubladze" for the treatment of acute encephalomyelitis and multiple sclerosis. This vaccine, which is produced and used in the Soviet Union, is given in two courses, each of divided subcutaneous injections of 24 ml. of the vaccine, or three courses of intracutaneous injections of a total of 5.2 ml. These courses of treatment may be repeated (Instruction*).

We have been unable to find that sera from patients in Northern Ireland with multiple sclerosis show any significant neutralization of the SV strain of E.H.A. virus. The results presented by Choubladze *et al.* (1956) showed that 9 out of 10 patients with multiple sclerosis had neutralization titres ranging from 269 to 2,564. We were unable to obtain information on the exact method of neutralization which was employed by Professor Choubladze and her associates, but the method we employed is the one commonly used to demonstrate antibody to rabies virus and similar to the techniques commonly used to demonstrate antibody to encephalitis viruses.

The results of the studies of Choubladze *et al.* (1956) indicated that E.H.A. virus was immunologically related to rabies virus. They considered that the virus was different from rabies, and they failed to find any Negri bodies in histological material (Choubladze and Gaidamovitch, 1956b). Our demonstration of Negri bodies in mice inoculated with the SV strain of E.H.A. virus and the immunological studies of Choubladze and Gaidamovitch (1956b) seem to indicate that E.H.A. virus cannot be differentiated from rabies virus. (It should be noted that no rabies virus had been handled in our laboratory prior to this investigation.)

Since we cannot find any relationship between the virus of E.H.A. and multiple sclerosis in Northern Ireland, and since this virus cannot be differentiated from that of rabies, there seems to be no rationale for using the "vaccine of Choubladze and Margoulis" in preference to any other rabies vaccine in the treatment of multiple sclerosis.

Choubladze and Gaidamovitch (1956a) claimed that "the vaccine of Margoulis and Choubladze" has produced amelioration in 30% of cases of multiple sclerosis, but Choubladze (personal communication from Dr. R. S. Allison) notes that while their vaccine helps one-third of treated patients it does not help those who have been ill for a long time. Numerous claims have been made for successful treatments for multiple sclerosis. In the assessment of any treatment it must always be remembered that spontaneous remission characterizes early cases. From Brickner's (1936) compilation of recorded results of various treatments of multiple sclerosis, Putman (1939) concluded that 665 out of 1,407 cases (47.5%) profited from the treatments. He also showed that 44% of fresh lesions in untreated patients are capable of a complete functional recovery. If it is assumed that patients usually seek a new form of treatment when a new lesion occurs it is perhaps not surprising that 47.5% of patients given any kind of treatment have been reported to show improvement in view of the 44% of spontaneous remissions (Putman, 1939). On this basis there is thus no evidence for the success of the "vaccine of Choubladze and Margoulis." Indeed, the use of this vaccine (formalized rabies-virus-infected rodent brain), which is given in multiple inoculations, might do harm.

*Instruction for the administration of the vaccine against acute encephalomyelitis and sclerosis multiplex. Souischimeaport, Moscow.

Summary

The SV strain of E.H.A. virus which has been used to prepare the vaccine of Choubladze and Margoulis for the treatment of multiple sclerosis appears to be rabies virus.

We were unable to demonstrate any specific neutralization of the SV strain of E.H.A. virus with sera from patients with multiple sclerosis.

Choubladze and Gaidamovitch's (1956a) claim for amelioration of 30% of patients with multiple sclerosis treated with this vaccine is of the same order as that of spontaneous remissions (44%) of fresh lesions in untreated patients.

The possible danger associated with the use of any rabies vaccine may make the use of the "vaccine of Choubladze and Margoulis" dangerous in the treatment of multiple sclerosis.

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AMISOMETRADINE, A NEW ORAL DIURETIC

BY

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Much importance is attached to the search for an orally active diuretic to support or replace parenteral mercurial preparations in the management of cases of heart failure. To date, all such drugs have had in common the disadvantage of poor gastro-intestinal tolerance when given in effective doses.

Of the active diuretics in the amino-uracil series of drugs, aminometradine ("mictine") has been most widely investigated (Kattus *et al.*, 1952; Platts and Hanley, 1956). In effective doses it has at least half the diuretic strength of mersalyl, but such doses produce epigastric discomfort, nausea, vomiting, or diarrhoea in almost 50% of patients; headache, tinnitus, and albuminuria are less common side-effects. Several chemically similar drugs have been studied, and amisometradine ("rolicton"*) is the most promising of them at present. In animals it has an equal or a better diuretic action than aminometradine, but causes far less vomiting; in both long and short trials it has been found relatively

*Kindly supplied by G. D. Searle and Co., Ltd.

free from toxic effects (Hambourger *et al.*, 1957; Van Arman *et al.*, 1957). Reports of three brief clinical trials in America were encouraging, and suggested that amisometradine was superior to all other oral diuretics (personal communications from H. Gold in February, 1956; M. G. Golder in June, 1956; and E. Settler in June, 1956).

The purpose of this paper is to report our own experience with amisometradine in the treatment of heart failure, its diuretic strength being compared with that of mersalyl, and particular attention being paid to the incidence of gastro-intestinal intolerance.

Method

Twenty patients who were admitted to hospital for treatment of heart failure were chosen for the trial. Sixteen of them had a raised venous pressure and oedema, and four had pure left ventricular failure. The aetiology was rheumatic in 11 cases, ischaemic in 7, and congenital in 2. Sixteen had previously been taking full doses of digitalis, and 12 had received regular injections of mersalyl in addition.

During the period of the trial digitalis was continued, dietary sodium was restricted to 1 g. daily, and the fluid intake was fixed at either 40 or 50 oz. (1,136 or 1,420 ml.) daily. The 24-hour urine output and body weight were measured daily and charted.

Test doses of amisometradine and mersalyl were given alternately to each patient at intervals of three to four days. The tests were grouped in pairs, so that each amisometradine test was accompanied by a mersalyl test in the same patient at only a short interval, during which time the patient's clinical condition had changed very little. To avoid influencing the results by the spontaneous diuresis which often occurs a few days after a patient is put to bed in hospital, the trial was not begun during the first 10 days of admission in a proportion of cases, and in the remainder amisometradine was administered first in one half, and mersalyl first in the other half. Six of the 20 patients came into the latter group, and

thus three pairs of tests were recorded which favoured one or the other drug. The errors in comparison of the drugs in these six patients individually were considered to balance out when comparison was made over the whole series.

Amisometradine was given in a dose of 400 mg. (one tablet) three times daily for two days. Administered in this way, the drug acts over a period of 48 hours (Fig. 1), and its diuretic effect was considered to be the excess of urine passed during this period. As already described in connexion with other amino-uracil derivatives (Spencer and Lloyd-Thomas, 1953; Platts and Hanley, 1956), the diuresis may not begin for 12 to 24 hours after the first dose is administered, and may continue for an equal time after the last dose. The 48-hour period of diuretic activity was therefore taken to be either the first and second days, as in Fig. 1, or the second and third days, as in Fig. 2, whichever yielded the greater quantity of urine. This selection of two out of the three days gave a figure slightly less than the total diuresis obtained, but no more rigid ruling served our purpose better.

In the case of mersalyl, a dose of 2 ml. intramuscularly was given, and the diuresis was considered to be the excess of urine passed during the 24 hours immediately following the injection.

The excess of urine passed was estimated in each case by subtracting from the output during the period of diuresis the output during the control period immediately preceding the test, during 48 hours in the case of amisometradine, and during 24 hours in the case of mersalyl. The changing physiological state of the patient prohibited use of a mean output calculated from all control days as a basis from which to measure diuresis.

The diuresis recorded in each test was expressed as a percentage of the output during the preceding control period, and this figure was called the diuretic index for that test. For example, if an amisometradine test resulted in an output of 140 oz. (3,975 ml.) over 48 hours, and the output during the preceding 48 hours was 80 oz. (2,270 ml.), then the diuresis was expressed as $140 - 80$, or 60 oz. (1,700 ml.), and the diuretic index as $60/80 \times 100$ or +75%. The diuretic index of each drug was averaged for each patient, and only these average indices were used in computing the results for the whole series.

Side-effects, if any, were recorded, and their specificity was verified. In most cases a daily specimen of urine was tested for albumin. Routine blood and full chemical and microscopic urine examinations were repeated at the end of the trial period.

Finally, three additional patients in need of diuretic therapy were given amisometradine 400 mg. three times daily for periods of 10 to 14 days, with repeated observation of their clinical response, the white blood cell count, blood urea, serum electrolytes, and urine.

Results

In each patient one or more pairs of amisometradine and mersalyl tests were performed. The table shows the average diuresis and diuretic index of each drug in each of the 20 patients. In six of them (Cases 6, 8, 9, 13, 14, and 18) the

FIG. 1.—Case 8. Urine output and weight, recorded daily in a man aged 43 with congestive heart failure previously untreated. Action of amisometradine and mersalyl compared. (Fluid intake 40 oz. (1,136 ml.) daily.)

FIG. 2.—Case 5. Urine output chart in a man aged 56 with congestive heart failure. Amisometradine and mersalyl compared. Action of amisometradine delayed 24 hours after administration. (Fluid intake 50 oz. (1,420 ml.) daily.)

results were influenced by the advantage given to the drug that was given first. The average figures at the foot of the table represent the results of 38 tests of each drug, and provide a direct measure of the diuretic strength of amisometradine in terms of that of mersalyl.

Diuretic Strengths of Amisometradine 400 mg. t.d.s., for Two Days, and Mersalyl 2 ml. Intramuscularly, Compared in 20 Patients

Case No.	No. of Tests	Average Diuresis				Diuretic Index (%)	
		Amisometradine		Mersalyl		Amisometradine	Mersalyl
		oz.	ml.	oz.	ml.		
1	1	44	1,250	36	1,023	+52	+90
2	4	31	880	18	511	+70	+69
3	5	34	966	34	966	+42	+84
4	1	32	909	42	1,193	+37	+78
5	2	45	1,278	34	966	+50	+100
6*	2	21	597	16	454	+29	+41
7	1	40	1,136	16	454	+50	+33
8†	3	37	1,051	80	2,272	+52	+220
9†	1	36	1,023	60	1,705	+51	+170
10	2	11	313	8	227	+48	+41
11	2	7	199	42	1,193	+10	+120
12	2	22	625	33	938	+35	+110
13*	1	47	1,335	30	852	+71	+71
14*	2	30	852	21	597	+27	+35
15	1	26	739	44	1,250	+33	+110
16	2	30	852	88	2,500	+49	+260
17	1	35	994	15	426	+35	+65
18†	1	10	284	44	1,250	+11	+150
19	2	12	341	70	1,969	+12	+190
20	2	19	540	14	398	+29	+39
Average		28	795	37	1,051	+41	+103

* Clinical condition improving rapidly; amisometradine given first.

† Clinical condition improving rapidly; mersalyl given first.

In 17 of the 20 patients the diuretic index of amisometradine ranged between +29% and +71%, indicating a satisfactory therapeutic response. In the remaining three it was relatively ineffective, with indices of +10%, +11%, and +12%. The average diuretic index of amisometradine in the 20 patients was +41%, compared with +103% in the case of mersalyl. In other words, 2.4 g. of amisometradine administered over a period of 48 hours had 40% of the diuretic potency of a single injection of 2 ml. of mersalyl. In four patients amisometradine appeared more effective than mersalyl, and this was consistently so on four occasions in Case 2.

The occasional delay in the action of amisometradine has already been mentioned, and is illustrated in Fig. 2. This occurred in about one-third of the patients, and was most marked in cases of severe congestive heart failure, becoming less conspicuous during recovery.

No side-effects attributable to amisometradine were seen in 15 of the 20 patients. Two developed mild nausea on the first day of administration only, but subsequently tolerated the usual dose. In one patient (Case 18) nausea was more severe, and recurred on each day of amisometradine therapy, associated on one occasion with vomiting. This patient had marked distension of the liver, and vomiting had been a prominent symptom of heart failure before admission. Reduction of the amisometradine dose by half improved tolerance, but produced little diuresis. In Case 17 transient mild diarrhoea occurred on the day following the single amisometradine test; unfortunately the test could not be repeated in this patient. Case 19, that of a woman with primary pulmonary hypertension, developed tinnitus and deafness on the second administration of amisometradine; this subsided within 12 hours, but subsequently recurred on two occasions after only 400 mg. of amisometradine, preventing further use of the drug.

In no case did albuminuria develop or increase during the trial. No toxic effect was detected by the full blood and urine examinations. Two patients (Cases 2 and 3) received total doses of 12 and 14.4 g. of amisometradine respectively over a period of six to seven weeks. Their recovery from heart failure was good, there were no side-effects, and the blood count, serum electrolytes, and urine remained unaffected throughout.

Continuous Daily Administration

The object of this trial was to find out whether amisometradine was an active diuretic in doses that were well tolerated. No attempt was made to establish the best scheme of dosage, but it seemed desirable to see whether the drug could be given daily without ill effect, and so this was tried in three patients. The first two were given amisometradine 400 mg. three times daily for 10 days, and their clinical progress suggested that a moderate diuretic effect had been obtained. A third patient in chronic heart failure was given mersalyl injections twice weekly only for the first fortnight, and amisometradine 400 mg. three times daily (together with one mersalyl injection weekly) for the second fortnight. The urine output chart (Fig. 3) shows a good diuretic response to

FIG. 3.—Case C. Urine output chart showing the result of adding amisometradine to the treatment of a woman aged 54 in chronic heart failure. Mersalyl twice weekly for the first two weeks, and once weekly with amisometradine 400 mg. t.d.s., for the second two weeks. (Fluid intake 40 oz. (1,140 ml.) daily.)

amisometradine given in this way. No side-effects were observed in these three patients, and no change could be detected in the blood or urine.

Discussion

Early in this study it became evident that amisometradine produced a significant diuresis in most patients with heart failure, and that gastro-intestinal intolerance was unusual. Many difficulties beset the measurement of the diuretic strength of a new drug, as discussed by Spencer and Lloyd-Thomas (1953), but these have been overcome to some extent in the present study by comparing the drug with the already familiar mersalyl. Paired doses of each drug given at short intervals permitted little change in the clinical state of the patient between tests. When such a change did occur, each pair of tests was balanced by another under similar circumstances, in which the order of administration of the drugs was reversed. The results of each test were made still more comparable by the expression of diuresis in the form of a diuretic index, taking into account the rate of urine flow immediately preceding the test.

The final outcome of the trial, that 2.4 g. of amisometradine had only 40% of the diuretic strength of 2 ml. of mersalyl, makes it clear that even the best oral diuretics cannot yet replace mersalyl in the treatment of acute or severe heart failure, but with improved tolerance and greater potency they are becoming increasingly valuable adjuncts.

Amisometradine proved to be greatly superior to amino-metradine in the matter of tolerance and was not less potent. In only one patient was nausea troublesome, and she was known to be prone to gastro-intestinal disturbance. The only

[illegible]