A COMPARATIVE TRIAL OF HEXAMINE HIPPURATE AND HEXAMINE MANDELATE IN PREVENTION OF RECURRENT INFECTION OF THE URINARY TRACT

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A Comparative Trial of Hexamine Hippurate and Hexamine Mandelate in Prevention of Recurrent Infection of the Urinary Tract

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DURING the past sixty years hexamine (methenamine) and its salts have been used extensively in the treatment of urinary-tract infection. In 1935, Rosenheim reported encouraging results in the treatment of the same condition with mandelic acid, and since then the mandelate salt of hexamine has been the most commonly used form of this therapy (Kolloff and Nelson, 1938). Hexamine exerts its bacterial action through the liberation of formaldehyde in an acid medium, the optimum pH being approximately 5·5, with a urinary output of less than 2000 ml. Recently, another salt of hexamine, hexamine hippurate, has been introduced (Gibson, 1970). This has a similar antibacterial spectrum to the mandelate and has been used in the treatment of chronic urinary-tract infection (Seneca *et al.*, 1967; Gerstein *et al.*, 1968). This salt was introduced after Bodell (1959) had shown that hippuric acid also has antibacterial activity. Seneca and Peer (1969) showed that the urinary level of formaldehyde produced by hexamine hippurate is higher than that due to hexamine or its mandelate salt.

A comprehensive review of hexamine preparations has recently been published (Katul and Frank, 1970). This concluded that hexamine hippurate demonstrated a significant antibacterial activity against four organisms: *Escherichia coli, Klebsiella aerobacter, Proteus mirabilis,* and *Pseudomonas aeruginosa.*

Although pH was not critical, effectiveness was increased by rendering the urine more acid. Katul and Frank found that provided the pH was less than 6 and that there was a high urine osmolality with a specific gravity greater than 10 10, hexamine salts were effective. These facts were also noted by Stamey (1968).

METHOD

All patients included in the study had to fulfil the following criteria:

(1) At least two previous episodes of bacteriologically confirmed lower urinary tract infection.

(2) Sterile urine at the time of admission to the study.

(3) No radiologically demonstrable renal lesion.

(4) No pelvic infection.

Patients were treated for six months: three months on one drug, followed by three months on the other. The preparation to be given first was determined by random selection: patients born on even dates starting with the

hippurate ('Hiprex') and those born on odd dates with the mandelate ('Mandelamine').

Dosage was: 'Hiprex' 1 G twice daily; 'Mandelamine' 1 G four times daily. (These were the dosages recommended by the manufacturers.)

No patients who fulfilled the criteria were refused; 95 per cent. were women, the average age being approximately 40 years. Patients who 'failed'

Reason	'Hiprex'	'Mandelamine'
Unable to take tablets	2	3
Reinfection of urine	2	3
Side-effects	1	–
Total	5	6

TABLE I.—Reasons for 'failure' in the 11 patients whose treatment was not crossed over

Result	No. of patients	
	'Hiprex'	'Mandelamine'
Success	67	53
'Failure'	6	20

$p = 0{\cdot}01$

TABLE II.—Analysis of results in the 73 who completed the trial (including re-entry patients)

on treatment due to reinfection were removed from the study, treated with a suitable antibiotic, and then re-entered on the alternative drug used in the trial. Similarly, patients who failed for other reasons—e.g. side-effects—were removed and then re-entered on the alternative treatment.

Patients were seen at monthly intervals, or sooner if complications occurred, when urinalysis was carried out and subjective and objective assessments made. These objective assessments were based on the following upper limits of normal parameters:

Albumin:	A trace
Red blood cells:	Nil
Leucocytes:	5 per cent. high power field in women.
	3 per cent. high power field in men.

RESULTS

Ninety-two patients who fulfilled the criteria were admitted to the study but 8 of these were withdrawn for reasons not related to treatment; a further 11 patients were not crossed over and are therefore not included in the analysis although separate results for these are shown in table I.

The number of treatments initiated in respect of patients who were crossed-over was 146: 73 on 'Hiprex' and 73 on 'Mandelamine'. The results are shown in table II. The difference between these results was significant ($p = 0{\cdot}01$). Success was defined as the maintenance of a sterile

urine throughout a three-month course. The reasons for failure are shown in more detail in table III.

Reason	'Hiprex'	'Mandelamine'	
Unable to take tablets	–	6	
Reinfection	5	7	(N/S)
Side-effects	1	6	
Forgot tablets	–	1	
	6	20	

TABLE III.—Reasons for 'failure' in the two regimens of treatment

Side-effect	'Hiprex'	'Mandelamine'
Gastric upset	2	1
Pruritus	2	1
Nausea	3	14
Vomiting	—	6
Stomach cramps	—	2
Difficulty in taking tablets	1	11
Unable to tolerate full dose	—	1
Allergic (skin) reaction	1	—
Diarrhoea	—	1
Anorexia	1	—
Indigestion	—	1
Abdominal discomfort	—	2
Dysuria and haematuria	—	1
Urgency	—	1
Increase in weight	1	—
Headaches	—	1
Depression	—	1
Backache	—	1
	11	45

TABLE IV.—Incidence of side-effects among the 73 patients who completed the trial

It will be noted that there is no significant difference between the two treatments with regard to prevention of reinfection. The differences in the number of failures on each treatment were due almost entirely to the inability to take tablets and the higher number of complications due mainly to disturbances of the gastrointestinal tract while on treatment with 'Mandelamine'. Most of the patients who were unable to take 'Mandelamine' tablets found that having to remember to swallow two tablets four times a day, day after day, week after week, for three months became extremely difficult, even intolerable.

A detailed list of side-effects reported during the study is shown in table IV. Nearly all of these were related to disturbances of the gastrointestinal tract. Very few of these were severe, and some patients were able to tolerate a reduced number of 'Mandelamine' tablets for a while whilst others

found taking the tablets with milk of some benefit. It is interesting that there was a higher incidence of disturbances of the gastrointestinal tract from 'Mandelamine' in spite of the enteric coating which is claimed to prevent the occurrence of this side-effect. Table V shows that there were significantly fewer patients who reported side-effects while on treatment with 'Hiprex' ($p = 0{\cdot}001$). This table also shows that in 27 patients there

	Number of patients		p
	'Hiprex'	'Mandelamine'	
Objective assessment of improvement	27	7	0·001
Side-effects	6	25	0·001

TABLE V.—Number of patients who showed improvement on objective assessment, together with the number of these who experienced side-effects

was objective improvement (in accordance with the criteria stated above) whilst on treatment with 'Hiprex', whilst seven patients showed objective improvement during treatment with 'Mandelamine'. There was a significant difference between these two results ($p = 0{\cdot}001$).

Subjective improvement also was studied, and 43 patients reported improvement while on 'Hiprex' and 13 while on 'Mandelamine'. Although these results are highly significant it is considered that they should be treated with reserve, since many of the patients were symptom-free at the start of treatment and that for a fair comparison a much larger number of patients would need to be studied.

DISCUSSION

Although antibiotics have rendered an outstanding service in the treatment of urinary-tract infection, they still have drawbacks: mainly the emergence of resistant strains and the incidence of occasionally severe side-effects.

It is mandatory that appropriate antibiotics to which the organism is sensitive should be used in acute urinary tract infections, but for prophylaxis when there is no lesion of the upper urinary tract increased use could be made of antibacterial drugs. It may be necessary to use such drugs as nitrofurantoin, nalidixic acid, ampicillin and trimethoprim on a long-term basis, but it is considered that antibacterials such as hexamine hippurate have a place in the prevention of recurrent urinary tract infection in those cases in which attacks are infrequent and of minimal virulence.

CONCLUSIONS

'Hiprex' (hexamine hippurate) and 'Mandelamine' (hexamine mandelate) were found to be satisfactory antibacterial drugs for the prevention of lower urinary-tract infection.

In this study, no significant difference was found between the reinfection rates when these agents were compared, but 'Hiprex' is considered to be preferable since the dosage is only two tablets a day, compared with eight with the other preparation.

The objective and subjective improvement during the treatment with 'Hiprex' was greater, and the incidence of side-effects was significantly lower.

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