EXCRETION STUDIES OF NITROFURANTOIN AND NITROFURANTOIN WITH DEGLYCYRRHIZINATED LIQUORICE

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Summary: Nitrofurantoin and nitrofurantoin with liquorice were given to healthy volunteers and patients suffering from urinary tract infections. The excretion rates of the drug, colony counts and side effects were studied in patients and excretion rates in the volunteers. The excretion rates of the drug were significantly higher in patients receiving the drug with liquorice and also side effects were minimal. There was no significant difference in the excretion rates of the drug with addition of liquorice in healthy volunteers.

Key words: Nitrofurantoin Liquorice urinary tract excretion infection

INTRODUCTION

Nitrofurantoin is a standard chemotherapeutic agent in the treatment of urinary tract infections. One of the distressing side effects is gastro-intestinal upset. Efforts to eliminate this effect without decreasing the bio-availability of the drug have been made in the past (1,2,8,9). The present study was undertaken to compare the urinary levels of nitrofurantoin obtained with deglycyrrhizinated liquorice and with plain nitrofurantoin.

MATERIAL AND METHODS

The study was made in 14 healthy volunteers and 12 patients. Healthy volunteers and patients were divided into two equal groups. Nitrofurantoin with liquorice and plain nitrofurantoin were given in a double blind randomized manner. The study consisted of estimating the excretion of the drug in both volunteers and patients. Estimation of the drug in urine was made by the method of Conklin and Hollifield (3). Estimation of the drug was made 6 hr after administration. In both the groups of volunteers and patients, the urine was analysed immediately or nitrofurantoin. The drug was given on empty stomach. In patients with urinary tract infection, colony counts were made before starting the treatment and on the 5th and 15th days of treatment. In the patients each time a fresh

midstream sample of urine was put up for culture within 1/2 hr of collection and bacterial colonies were counted subsequently. The culture was done on the three consecutive days and the mean of these bacterial colony counts was taken as representative of bacteruria.

RESULTS

Volunteers :

The urinary excretion of the drug in volunteers receiving plain nitrofurantoin ranged from 41.29 *mg* to 62.0 *mg* with a mean of 46.3 *mg* (±1SD 8.59). The excretion of the drug in volunteers receiving nitrofurantoin with liquorice ranged from 27.29 *mg* to 51.0 *mg* with a mean of 38.94 *mg* (±1SD 7.1). The excretion values in the two groups were statistically not significant.

Patients :

The urinary excretion of the drug in patients receiving nitrofurantoin with liquorice ranged from 33.81 *mg* to 56.2 *mg* with a mean of 41.95 *mg* (±1SD 7.52). The excretion of the drug in patients receiving plain nitrofurantoin ranged from 30.5 *mg* to 39.9 *mg* with a mean of 36.98 *mg* (±1SD 3.4). The difference in the excretion of the drug in the two groups was statistically significant ($P<0.01$) when urine samples were estimated for nitrofurantoin at 6 hr intervals

The difference in excretion of the drug in patients and volunteers receiving plain nitrofurantoin was not statistically significant. Also there was no statistically significant difference in the excretion of the drug in patients and volunteers receiving nitrofurantoin with liquorice.

Bacterial colony counts :

In both the groups, patients had moderate to severe urinary tract infection as was shown by the initial colony counts. The change in the colony counts on treatment was as follows : -

Nitrofurantoin with liquorice : The urine became sterile in 3 patients by 5th day and 2 patients by 15th day and 1 patient had persistant infection.

Plain nitrofurantoin ; The urine became sterile in 1 patient by 5th day, 4 patients by 15th day and 1 patient continued to show no change (Table I).

Side effects :

Nausea was present in 3 patients receiving nitrofurantoin with liquorice, whereas 5 out of 6 patients receiving plain nitrofurantoin had nausea, burning sensation of the stomach and vomitings (Table II).

TABLE I : Colony counts before and at 5 and 15 days of treatment.

Sl. No.	Drug used	Type of organism	No. of colonies per ml of urine		
			Before	5th day	15th day
1.	Nitrofurantoin with liquorice	KL	1.4×10^4	Sterile	Sterile
2.	,,	E. Coli	7×10^{10}	Sterile	Sterile
3.	,,	E. Coli	1×10^6	Sterile	Sterile
4.	,,	E. Coli	6×10^9	4×10^7	Sterile
5.	,,	Prot	1.5×10^7	1.5×10^6	5×10^5
6.	,,	KL	1.08×10^7	2.8×10^6	Sterile
7.	Plain Nitrofurantoin	E. Coli	8×10^6	Sterile	Sterile
8.	,,	E. Coli	2×10^5	2×10^3	Sterile
9.	,,	E. Coli	6.9×10^{10}	8×10^8	Sterile
10.	,,	KL	1×10^{10}	5×10^8	5×10^8
11.	,,	Prot	9×10^8	4×10^7	Sterile
12.	,,	E. Coli	7×10^{10}	1×10^9	Sterile

TABLE II : Side effects of the two modalities of treatment.

	Nitrofurantoin + Liquorice	Nitrofurantoin
Nausea	2	2
Vomiting	—	1
Burning sensation ABD	1	4
Headache	1	4
Loss of appetite	1	1

DISCUSSION

Nitrofurantoin is a weak acid and the excretion is affected by fluctuations in the urinary pH. Food has the greatest absorption enhancing effect on the drug (1). Different studies have been conducted to evaluate the effect of addition of substances to nitrofurantoin on its absorption and excretion. The microcrystalline form is absorbed more than the macrocrystalline form, but both the forms are absorbed more on a full stomach (7). Consequently the mean percentage excretion rates of the drug are greater after taking food

than on an empty stomach, and it is possible for a greater fraction of the drug to be dissolved in the gastric fluids prior to its emptying in the duodenum where nitrofurantoin absorption is optimal (2).

Various procedures were adopted to decrease the gastric irritating properties of nitrofurantoin. Methyl cellulose has been used as an agent to decrease the gastric irritation and also as the medium of the drug (9). It causes a reduction in the dialysis rate both in the drug solution as well as drug suspension (1). But the dialysis rate was less pronounced in methyl cellulose solution than in drug suspension water. The reduction in the dialysis rate of the drug solution containing polymer is thought to be due to the possible formation of a drug complex. There is also high viscosity of the drug suspension surrounding the drug particles, leading to the possible creation of a diffusion layer.

Liquorice has been added to nitrofurantoin in order to decrease the side effects. Many workers reported the ulcer healing properties of deglycyrrhizinated liquorice in gastric and duodenal ulcers (4,11). Subsequent studies comparing it with placebo have not substantiated that the drug would either decrease the acid levels in duodenal ulcer or healing of gastric ulcers (5). Henman (6) found carbenoxolone superior to deglycyrrhizinated acid in reducing pepsin activity in anaesthetised pylorus ligated rats and attrributed this action to plasma binding mechanism of the drugs. But Whitehouse *et al.* (10) in their *in vitro* studies detected benzoic acid (0 3 - 0 (B - carboxy - propionyl) 18 - B - glycerrhietamidio to have more powerful plasma binding capacity for pepsin. Probably liquorice also causes amelioration of symptoms of gastric irritation and nausea by its demulcent action. The demulcent property of the drug can be used to overcome the gastric irritation produced by nitrofurantoin. It is seen from the results that the side effects were minimal in patients receiving plain nitrofurantoin. The excretion values of the drug were not affected by the addition of liquorice either between healthy volunteers or between healthy volunteers and patients. It is seen from the study that in the presence of infection, the excretion of the drug was significantly higher, when liquorice was added. The possible inference that can be derived from this study is that at 6 hr intervals significantly increased amounts of nitrofurantoin are present when nitrofurnatoin with liquorice is given than nitrofurantoin plain and that studies are required for these differences to be translated into clinical significance.

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