DISPOSITION KINETICS OF SULPHADLAZINE IN NORMAL AND DIABETIC RABBITS

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Abstract

Influence of alloxan induced metabolic disorder on the biodisposition kinetics of a weakly acidic drug sulphadiazine was investigated in rabbits. In 12 rabbits, mean ± SD blood pH was 7.45 ± 0.05, plasma glucose 123± 10.6 mg %, plasma total lipids 336 ± 124 mg % and plasma urea 36 ± 6 mg %. After treatment with 150 mg/kg alloxan intravenously the blood pH was 7.20 ± 0.06, plasma glucose 393 ± 80.3. total lipids 532 ± 181 and plasma urea was 48 ± 10 mg %. Disposition kinetics showed that the plasma concentration of sulphadiazine was significantly (P<0.01) higher in normal condition when compared with that of metabolically altered. The zero-time plasma concentration was significantly (P< 0.01) higher, apparent volume of distribution and total body clearance were significantly (P< 0.01) lower in the normal than in the metabolically altered condition of rabbits. Elimination rate constant and the half-life did not reveal any significant difference in the normal and metabolically altered conditions. These studies demonstrate that the clinical biochemical conditions can influence the disposition kinetics and fate of weakly acid, and possibly of the weakly basic drugs. Therefore, the therapeutic standards of the drugs need be verified in the condition in which the drugs are to be employed clinically (JPMA 39; 51, 1989).

INTRODUCTION

The sustenance of life is dependent upon the availability of energy derived by the metabolic processes. Disruption of these processes during metabolic disease are accompanied by changes in the milieu interieur of the body. Alterations in the biochemical environments of the body influence the biodisposition and fate of drugs which are either weak acids or weak bases. Such a pH dependent partitioning have implications for biodisposition and fate of drugs. For example alloxan destroys pancreatic beta cells, develops hypoinsulinemia and hyperglycaemia. This is accompanied by glycosuria, polyuria, lipaemia, ketonaemia, acidaemia, polydipsia and polyphagia. Sulphadiazine is a weakly acidic antibacterial drug, well suited for the study of disposition in normal and metabolically altered states. Therefore, the present study was undertaken to investigate the influence of alloxan induced metabolic alterations on disposition kinetics of sulphadiazine in rabbits.

MATERIALS AND METHODS

The experimental rabbits were maintained at the animal house, Department of Physiology and Pharmacology, University of Agriculture, Faisalabad. The rabbits belonged to an inbred stock. Their average body weight was 1.69 kg (range 1.49 to 1.82 kg). All the animals were clinically healthy adult females. The animals were fed with the green fodder (luscern) and water was provided all the times in cages. The blood samples from the jugular vein were collected in heparinised centrifuge tubes. The pH of blood was measured immediately after collection by a pH meter (Labsco) at 37°C. The blood was centrifuged and plasma was separated for the measurement of biochemical parameters and assay of sulphadiazine. Plisma glucose, total lipids and urea were estimated by the kit methods of Merck1. In
normal rabbits, disposition kinetics of sulfadiazine was investigated following a single intravenous injection of 50 mg/kg dose of 2.5 per cent, in physiological saline solution, in marginal ear vein of each animal. A control blood sample was collected before the administration of sulfadiazine. The blood samples were collected at 5, 10, 15, 30, 60, 120, 180, 240, 300, 360, 420 and 480 minutes after the drug administration. Plasma was separated and stored until analysis. The concentration of sulfadiazine in the plasma was measured as free amine spectrophotometrically. The plasma concentration of drug versus time data were used for determination of disposition kinetics parameters with the help of a programmable calculator TI-59 (Texas Instruments Inc.) using one-compartment kinetic model programme. After determination of disposition kinetics of sulfadiazine in normal state, the rabbits were maintained for 10 days for elimination of the drug. At the end of this period, each rabbit was injected a 2 per cent solution of alloxan in physiological saline at the dosage rate of 150 mg/kg. Following alloxan injection, blood glucose of each rabbit was measured daily until the level exceeded 300 mg per cent and the animal was considered hyperglycaemic. The blood of hyperglycaemic animals was drawn to measure the biochemical parameters as described above. The alloxan treated metabolically altered rabbits were used for the study of biodisposition of sulfadiazine by the same procedure as has been described earlier for the normal rabbits. The mean ± SD values were calculated for each of the biochemical and disposition kinetics parameters. Comparison of the biochemical and disposition kinetics parameters in both the conditions was done by the students t-test for paired data.

RESULTS

Results showing body weight, blood pH, plasma concentration of glucose, total lipids and urea in normal rabbits are presented in Table 1.
The students t-test value revealed highly significant (P<0.01) differences in body weight and all the biochemical parameters measured before and after alloxan treatment of the rabbits. A comparison of sulfadiazine plasma concentration in normal and alloxan treated metabolically altered condition of rabbits is shown in Table II.

<table>
<thead>
<tr>
<th>Biochemical parameters and units</th>
<th>Normal (Mean ± SD, n = 12)</th>
<th>Alloxan treated (Mean ± SD)</th>
<th>Students t-test value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight kg</td>
<td>1.69 ±0.12</td>
<td>1.44 ±0.14</td>
<td>4.45**</td>
</tr>
<tr>
<td>pH</td>
<td>7.45 ±0.05</td>
<td>7.20 ±0.06</td>
<td>11.7**</td>
</tr>
<tr>
<td>Glucose mg%</td>
<td>123 ±10.6</td>
<td>393 ±80.3</td>
<td>11.5**</td>
</tr>
<tr>
<td>Total lipids mg%</td>
<td>336 ±124</td>
<td>532 ±181</td>
<td>3.10**</td>
</tr>
<tr>
<td>Urea mg%</td>
<td>36 ±6</td>
<td>48 ±10</td>
<td>3.44**</td>
</tr>
</tbody>
</table>

** Highly significant difference (P<0.01).
The values of students t-test revealed highly significant (P < 0.01).
TABLE III. Mean ± SD of disposition kinetic parameters of Sulfadiazine in Normal and Alloxan treated metabolically altered Rabbits following Intravenous Administration of 50 mg/kg dose.

<table>
<thead>
<tr>
<th>Kinetic parameters and units</th>
<th>Mean ± SD (n=12)</th>
<th>Students t-test value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β µg/ml</td>
<td>253±13</td>
<td>205±10</td>
</tr>
<tr>
<td>β per min</td>
<td>0.0066±0.0004</td>
<td>0.0069±0.0006</td>
</tr>
<tr>
<td>t(0.5) min</td>
<td>106 ± 6</td>
<td>102 ± 10</td>
</tr>
<tr>
<td>Vd 1/kg</td>
<td>0.20±0.01</td>
<td>0.24±0.01</td>
</tr>
<tr>
<td>TBC ml/min/kg</td>
<td>1.30±0.08</td>
<td>1.67±0.09</td>
</tr>
</tbody>
</table>

N.S= None significant, ** Highly significant difference (P<0.01).

The biodisposition kinetic parameters have been compared with the students t-test values. The zero-time plasma concentration (B), was significantly (P<0.01) higher while apparent volume of distribution (Vd) and total body clearance (TBC) were significantly (P< 0.01) lower in the normal rabbits when compared with the ailoxan treated metabolically altered rabbits.

DISCUSSION

Metabolic alteration produced by the destruction of beta cells in pancreas by intravenous injection of alloxan, is comparable to the clinical condition of diabetes. After treatment with alloxan, the rabbits showed excessive drinking of water and apparent lack of energy manifested by the weakness of animals. The rabbits showed an increase in the rate of urine flow as a result of urinary excretion of glucose which increased the renal tubules luminal osmotic pressure and caused diuresis. The metabolically altered rabbits also showed a significant (P<0.01) reduction in the body weight probably due to enhanced catabolic activities. The blood pH of rabbits before metabolic disorder (normal condition) was significantly (P< 0.01) higher than the pH recorded in the metabolic disorder. Such a reduction in the blood pH has been recorded in dogs. Metabolic acidosis is caused by increasing quantities of ketone bodies neutralised by the buffers in body fluids up to certain threshold, above which ketonaemia will result in a decrease in blood pH. Metabolic acidosis is caused by a decrease in the bicarbonate fraction with either no change or relatively small change in the carbonic acid fraction. This is the most common, classic type of acidosis which results due to ketosis and some other clinical conditions.
conditions. Plasma total lipids in the normal rabbits were significantly (P < 0.01) lower than the alloxan post-treatment values during metabolic disorder. A similar increase in the triglycerides levels have been recorded in dogs. The reversal of triglyceride storage process in fatty tissue, lipolysis and additional fat mobilisation are responsible for the rise in blood lipid contents. Protein metabolism is also altered during metabolic disorders. However, plasma proteins did not reveal any significant change in the normal and metabolically altered dogs. However, in rabbits alloxan induced metabolic disorder significantly (P < 0.01) increased the blood urea levels. An enhancement of catabolic activity during metabolic disorders is not uncommon, therefore, a rise in endogenous plasma urea be attributed to this condition. Plasma concentration of sulfadiazine in rabbits before and after induced metabolic disorder depicted a straight line on the semiogarithmic scale against time which indicated that the biodisposition kinetic parameters can be best described by one-compartment model kinetics. The plasma concentration of sulfadiazine in rabbits before and after treatment with alloxan revealed a highly significant (P < 0.01) difference. The concentration was lower in state of metabolic disorder. Sulfadiazine is a weakly acidic drug (pKa = 6.5). A reduction in the blood pH favours unionization and passage of sulphadiazine across the biomembranes. The pH dependent partitioning of the weakly acidic and basic drugs is a well established phenomenon. However, such a difference in the plasma concentration of sulfadiazine was not recorded in the dogs. Because of this difference in the concentration of sulfadiazine in rabbits, zero-time plasma concentration of the drug was significantly (P < 0.01) higher in normal, and lower in metabolically altered condition of the rabbits. The apparent volume of distribution in normal rabbits was significantly (P < 0.01) lower than in the metabolically altered condition and this is attributable to lower zero-time concentration in the latter condition. However, in dogs the volume of distribution was lower because of higher value of zero-time plasma concentration in the metabolically altered condition. Total body clearance was significantly (P < 0.01) higher in metabolic alteration in rabbits when compared with the values in the normal pre-alloxan treatment values and this observation is very similar to the observation in dogs. In the alloxan treated metabolically altered rabbits, a decrease in blood pH is favourable for the unionization of the drug. The unionized species of the drug can easily cross the biomembranes of drug eliminating organs. The urine pH was not recorded during these studies; however, the change in urine pH occurs only in extreme metabolic disorder as the acidic ketones are largely buffered by ammonia or by fixed bases. Assuming insignificant alterations in the urinary pH, the high rate of urine flow prevented any possible back diffusion and caused high elimination or total body clearance of the drug under metabolic disorder. In view of the significant influence of the alloxan induced metabolic disorder on the biodisposition kinetics of weakly acidic sulfadiazine it is assumed that similar differences ought to exist for the weakly acidic or basic drugs in various metabolic disorders. Therefore, there is a need for the adjustment of the dosage regimen under such clinical conditions.

REFERENCES