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Short communication

Acetazolamide for alkalinisation of urine in patients receiving high-dose methotrexate

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Summary. Acetazolamide, 500 mg 6 hourly, has been used to alkalinise the urine in patients receiving high dose methotrexate. A urinary pH of >7.5 was achieved in every cycle (13 cycles in 10 patients). In 6 cycles a single supplementary dose of sodium bicarbonate was necessary. Plasma methotrexate levels fell satisfactorily at 24 and 48 h. Acetazolamide is a simple and effective method of achieving urinary alkalinisation with advantages over oral and intravenous bicarbonate.

Introduction

High-dose methotrexate (HDMTX) is included in many chemotherapy protocols for the treatment of osteosarcomas and other primary malignant bone tumours [2]. It has also been used at moderately high doses in the treatment of non-Hodgkin's lymphoma and of CNS relapse in lymphomas and teratomas [3]. Methotrexate and its 7-hydroxy metabolite are poorly soluble in acidic urine; if precipitation in the renal tubule occurs, it may lead to acute renal failure [4, 7]. To prevent this, the urine is alkalinised so as to keep the urinary pH above 7.5. For this purpose, oral sodium bicarbonate has traditionally been used, with i.v. administration being required if the urinary pH falls below 7.5. Oral sodium bicarbonate is unpalatable and is often refused by patients, necessitating the more frequent use of i.v. sodium bicarbonate, which requires hospitalisation. Acetazolamide is a carbonic anhydrase inhibitor that alkalinises urine by the inhibition of tubular-cell carbonic anhydrase, leading to a lack of reabsorption of tubular bicarbonate through the prevention of hydrogen ion synthesis in tubular cells. This inhibitor has occasionally been added to sodium bicarbonate regimens to assist in urinary alkalinisation during HDMTX administration, but its value as a single agent has not been assessed. Since the drug can be taken orally, it may have advantages over sodium bicarbonate. This study was therefore designed to assess the effect of acetazolamide on urinary alkalinisation during HDMTX administration.

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Patients and methods

Ten patients receiving HDMTX for osteosarcoma were studied. During the period of study, the 10 patients received 13 cycles of HDMTX (1 cycle in 7 subjects and 2 cycles in 3 cases). Patients were hydrated with 500 ml 0.9% sodium chloride over 30 min, followed by 8 g/m^2 HDMTX in 5% glucose over 6 h, followed by 1 l 0.9% sodium chloride alternating with 5% glucose given over 6 h for at least 36 h. Acetazolamide at a dose of 500 mg was given at the start of the HDMTX infusion and then at 6-h intervals until the 48-h methotrexate level was determined. The drug was given orally unless vomiting occurred. The pH of all urine voided was tested with Ames Labstix. If, in spite of these measures, the urinary pH was <7.5, sodium bicarbonate was given i.v. in 500 ml 1.26% solution over 30 min. Methotrexate levels were measured at 20 h and 44 h and folinic acid was started at 24 h and continued every 6 h according to the plasma levels. No oral sodium bicarbonate was given.

Results

Urinary alkalinisation with acetazolamide resulted in a pH value of >7.5 in all patients. The majority required either no i.v. bicarbonate (38%) or one infusion (46%). In no case did renal failure occur. The mean urinary pH is shown in Fig. 1. The urinary pH tended to fall at between 13 and 35 h and i.v. bicarbonate was occasionally given during this period. The mean pH fell to a nadir of 7.5 at 31–33 h after the start of methotrexate treatment. The 44-h concentration of methotrexate reached levels that did not necessitate prolonged folinic acid rescue (Fig. 2).

Discussion

Methotrexate is nephrotoxic at doses of $\geqslant 150$ mg/m^2. Its solubility increases in alkaline urine, thus preventing renal toxicity secondary to precipitation in the renal tubule. Al-

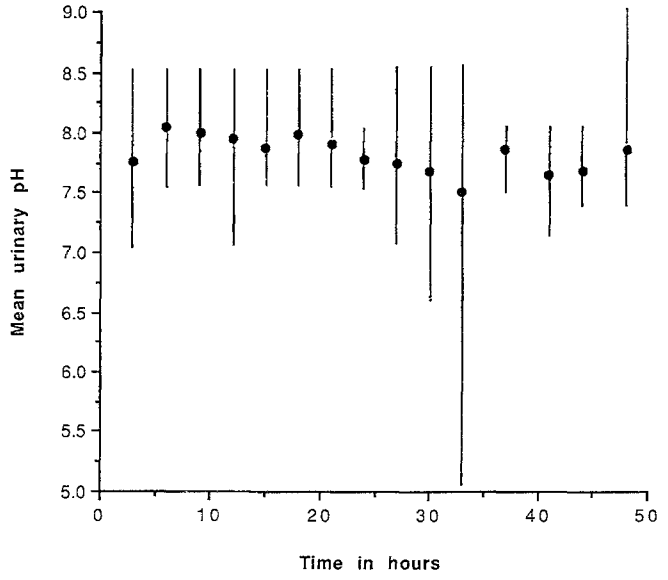

Fig. 1. Mean urinary pH and range measured in 10 patients following urinary alkalinisation with acetazolamide

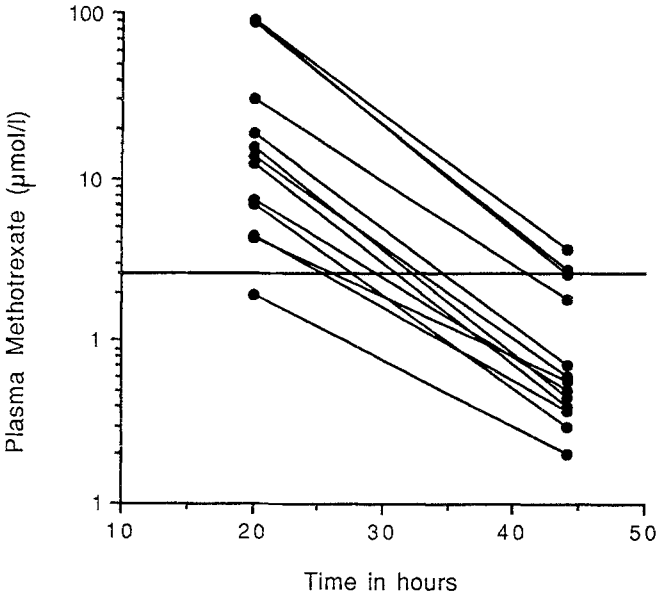

Fig. 2. Plasma methotrexate levels at 20 and 44 h. The *horizontal bar* indicates the limit of concentration above which folinic acid rescue is necessary

kalinisation of urine has enabled the safe administration of methotrexate doses of up to 50 g, even to the point of delaying equimolar rescue with folinic acid until 48 h after drug treatment [6]. Prophylactic urinary alkalinisation has been recommended in several protocols using intermediate doses of methotrexate [3, 5].

Acetazolamide has previously been used for alkalinisation, but only in addition to $NaHCO_3$ and at low doses (250–500 mg/day) [1, 6]. In the present study, starting at the onset of methotrexate treatment, at a much higher dose than that previously used (2 g/day). It was well tolerated orally, adequate and continuous alkalinity was maintained in over one-third of the treatment cycles without requiring $NaHCO_3$ administration, and a satisfactory decrease in methotrexate levels at 20 and 44 h was achieved. The maintenance of continuous alkalinity is particularly important when the intervals between voiding may be long, e.g. overnight, after which a low morning urinary pH may reflect many hours of production of acidic urine. The lowest pH occurred at 31–33 h, during which period $NaHCO_3$ was most likely to be needed. Only one treatment cycle required $NaHCO_3$ in the first 24 h, indicating the efficacy of acetazolamide over the period during which methotrexate levels were at their highest and the risk of renal damage therefore the greatest. Acetazolamide also has the advantage of being a diuretic in its own right, therefore helping to maintain urinary output. Acetazolamide is a non-competitive inhibitor of carbonic anhydrase. Its absorption is rapid, with peak plasma levels being attained within 2 h of administration. For this reason, its administration before HDMTX is probably unnecessary, especially when HDMTX is given by prolonged infusion.

The disadvantages of acetazolamide administration are few: it is costly if given intravenously, and it leads to alkalinisation of the urine at the expense of lowering serum bicarbonate levels, which inevitably means that its ability to alkalinise urine for prolonged periods of time (>48 h) when given alone is limited and cannot be overcome by increasing the dose. In such cases, i.e. when excretion of methotrexate is prolonged, the use of additional $NaHCO_3$ is inevitable.

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