Pefloxacin in adriamycin induced nephrotic syndrome in the rat

Z. Korzets, A. Pomeranz, E. Golan and J. Bernheim

Department of Nephrology, Meir General Hospital, Kfar Saba and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Background. Pefloxacin, a fluorinated 4-quinolone, has recently been advocated as a first-line treatment for minimal-change nephropathy (MCN) or focal segmental glomerulosclerosis (FSGS). To further evaluate this issue we have utilized an animal model resembling human MCN, namely adriamycin-induced nephrotic syndrome in Wistar male rats.

Methods. Adriamycin at a dose of 7 mg/kg was injected intravenously to all rats at day zero. Rats were divided into two groups: group A (n=20) given only water served as the control group while group B (n=19) was administered pefloxacin at 150 mg/kg. At days 7, 14, 21 and 28, the rats were placed in metabolic cages and daily proteinuria determined.

Results. The nephrotic syndrome developed in all rats within 7 days of adriamycin administration. At day 7, proteinuria in group B was 173 ± 78 vs 423 ± 626 mg/day in group A, P < 0.02, but thereafter at days 14, 21 and 28, no significant difference in urinary protein excretion was noted.

Conclusions. These results suggest that in this animal model of NS mimicking human MCN, pefloxacin’s antiproteinuric effect is only of a mild and transitory nature. In view of the above data and the overall results in human patients (detailed herein), the use of pefloxacin as definitive treatment of the NS cannot be recommended.

Key words: adriamycin, nephrotic syndrome, rat, pefloxacin

Introduction

The use of pefloxacin as a possible definitive treatment for idiopathic nephrotic syndrome, either minimal-change nephropathy (MCN) or focal segmental glomerulosclerosis (FSGS), was first proposed by Pruna et al. [1]. In their preliminary communication, favourable results (partial to complete remission) were obtained in three patients administered pefloxacin for 15–30 days. Berthoux et al. [2] reported on a series of six patients with nephrotic syndrome due to various causes in whom a significant reduction of proteinuria was seen in three and a complete remission in one. Notably, this latter case occurred in a 15-year-old boy with MCN. In contrast, other authors have reported no improvement or reduction of proteinuria, emphasizing, on the other hand, the drug’s toxicity [3–5]. Severe side-effects such as tenosynovitis, arthralgias with joint effusions, raised intracranial pressure, and acute interstitial nephritis were documented [3,4]. Thus, pefloxacin’s place in the treatment of idiopathic nephrotic syndrome is, to say the least, controversial.

In an attempt to evaluate the drug’s efficacy, we have studied its action in an animal model of the idiopathic nephrotic syndrome, i.e. in rats with adriamycin nephropathy. This model is characterized by morphological changes resembling human MCN or FSGS [6,7].

In a preliminary study utilizing a small number of rats [8], an antiproteinuric effect of pefloxacin at a dose of 150 mg/kg was demonstrated. However, a similar reduction of proteinuria was found with vitamin C (the ascorbate vehicle of pefloxacin) at a dose of 7 mg/kg. In the present study, we therefore extended our investigations using a larger animal population followed up for a 1-month period.

Subjects and methods

Experiments were performed using 39 age-matched male Wistar rats of mean body weight 200–300 g, fed standard laboratory chow (0.35 g NaCl, 20 g protein) and allowed tap water ad libitum. In all rats, adriamycin (7 mg/kg) was administered intravenously via a superficial femoral vein under light ether anaesthesia.

The rats were divided into two groups: group A (n=20) given only water ad libitum served as the control group and group B (n=19) was given pefloxacin (per drinking solution) at an average dose of 150 mg/kg beginning at day zero. All the rats were placed in metabolic cages at days 7, 14, 21 and 28 and daily urine volume and proteinuria measured. At day 28, the animals were sacrificed and blood was drawn for the measurement of serum creatinine and albumin.

Statistical analysis was performed using the Student’s t

Correspondence and offprint requests to: Prof. J. Bernheim, Department of Nephrology, Meir Hospital, Kfar Saba 44281, Israel.

© 1997 European Renal Association–European Dialysis and Transplant Association
test and Mann–Whitney test, as appropriate. Results are expressed as the mean ± SD.

Results

Table 1 shows the results obtained. As expected, all the rats developed nephrotic range proteinuria as of day 7. Mean serum creatinine (0.57 ± 0.08 and 0.6 ± 0.08 mg/dl) and mean serum albumin (2.37 ± 0.45 and 2.68 ± 0.27 g/dl) did not differ between the two groups. The only significant difference in proteinuria was evident at day 7, being 423 ± 656 vs 173 ± 78 mg/day in groups A and B respectively (P < 0.02). Thereafter, proteinuria in group B increased and similar levels of protein excretion were seen at days 14, 21 and 28.

Mortality rates and percentage delta decrease in body weight were similar between groups (results not shown).

Discussion

The pathogenesis of the nephrotic syndrome due to MCN or FSGS has not been clarified. It has, however, been associated with the altered production of various cytokines—excess of tumour necrosis like factors [9], decreased circulating interleukin-2 [10], and oversecretion of interleukin-1 [11]. Pefloxacin has been shown to possess immunomodulatory properties. In vitro, an antiproliferative effect on lymphocytes and monocytes has been demonstrated [12]. The drug increases interleukin-2 mRNA but decreases IL-2 receptor concentration [13]. A rational explanation could therefore be given for a beneficial effect of pefloxacin in MCN/FSGS.

In its early stages, adriamycin-induced nephrotic syndrome in the rat, the animal model we used, resembles MCN in the human, both biochemically and morphologically. In a preliminary experiment [8], findings seemed to suggest an antiproteinuric effect of pefloxacin at a dose of 150 mg/kg. However, a similar reduction of protein excretion was found by vitamin C (the ascorbate vehicle of pefloxacin) at a dose of 7 mg/kg. To further explore the effect of pefloxacin, we carried out the present study in an attempt to validate the antiproteinuric action of the drug in a larger number of rats. We were only able to show a significant, though mild and transient, decrease of proteinuria at day 7. Only one other animal study on the same model of adriamycin nephropathy has been performed to evaluate the effect of pefloxacin on urinary protein excretion [14]. The protocol of this prior study, however, differed from the one we had chosen. Female rats were used whereas we studied male rats and the dose of intravenous adriamycin was 5 mg/kg compared to the 7 mg/kg we employed. Furthermore, we administered pefloxacin beginning on the day of injection of adriamycin. In contrast, in the study of Zima [14], administration of pefloxacin was only started 3 weeks after the injection of adriamycin. Proteinuria was then determined at weeks 3 and 6.

Pefloxacin was not able to decrease established proteinuria in nephrotic rats. Nevertheless, compared to the untreated group, it prevented a further increase in protein excretion during the 3 weeks of its administration, suggesting a sustained beneficial effect. The difference from our results may be explained by the fact that we employed male rats which had been given a higher dosage of adriamycin. Male rats develop more severe proteinuria [15] and castration confers a protective effect on the development of proteinuria in uninephrectomized male Wistar rats [16]. In our animal model, the antiproteinuric effect of pefloxacin was only of a mild and transient nature.

Experience with the drug in humans is limited. Following the initial communication [1] several reports were published confirming or refuting the observation [2–5]. Altogether, 26 patients have been administered the drug, 22 of whom had either MCN or FSGS, usually steroid resistant. The overall response rate (partial or complete remission) was 26.9%. Although this response rate might be considered acceptable under certain conditions, the indication must consider the high incidence of severe effects [3,4]. Our results in this particular experimental model, do not support the notion that pefloxacin is a useful antiproteinuric drug. Although it is difficult to extrapolate animal data to humans, in view of the presently published clinical reports, the use of pefloxacin as a first-line treatment of the nephrotic syndrome in MCN/FSGS cannot be recommended.

References

7. Podjarny E, Rathaus M, Bernheim J et al. Captopril but not


Received for publication: 20.3.96
Accepted in revised form: 17.10.96