INFLUENCE OF ACUTE URAEMIA ON PERCUTANEOUS ABSORPTION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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The influence of uraemia on percutaneous absorption of three model drugs (diclofenac, ibuprofen and indomethacin) which are eliminated entirely via nonrenal route was investigated in the rats. Following day after bilateral nephrectomy (BUN levels were between 30–50 mmol/l), gel ointment containing drugs under test was applied on the abdominal site of the skin. Comparing with the sham operated controls the percutaneous absorption significantly decreased in all three challenged substances. Influence on percutaneous absorption of indomethacin was investigated more in depth as this compound can serve as a model for other nonsteroid anti-inflammatory drugs. The 50 mmol/l concentration of urea (equal to uraemia) added to the gel ointment did not influence percutaneous absorption while 10 % concentration of urea decreased percutaneous absorption of indomethacin approximately 5 times. Solubility of indomethacin increased in the presence of 10% urea in the gel more than two times. Elimination ratios Q_0 were estimated to find if there is any effect on pharmacokinetics linked directly to the renal elimination. None of such changes were observed.

INTRODUCTION

The increase of BUN (blood urea nitrogen) is besides of other parameters one of the most pronounced signs of the renal failure. Many papers have dealt with this clinically important subject, reviewed e. g. in the parts of the Brenner and Rector's monograph[1], Gibaldi and Prescott's Handbook of clinical pharmacokinetics, Section III[2] or Rowland and Tozer's Clinical Pharmacokinetics[3]. In the severe renal failure urea can create precipitates on the skin surface. It is also possible to find increased urea concentration in the skin layers. Urea is a physiological component of NMF (natural moisturising factor) of the skin. Owing to its mild keratolytic effect urea is used in the topical drug formulations[4]. Urea and its analogues were also studied as possible candidates to accelerate percutaneous absorption of drugs (Wong et al.[5], Williams and Barry[6].

Philosophy of following experiments is based on above mentioned experiences. We have not found any report dealing with the changes of percutaneous drug absorption under the conditions of concomitant uraemia. Our research was conducted with the aim to answer following questions: Are there any changes in percutaneous absorption of examined drugs in uraemia? What kind and extend of these changes can be expected? The drugs selected in these experiments are eliminated entirely via non renal route, to exclude direct effect of renal failure on pharmacokinetics. Comparison of pharmacokinetics after i. v. application was investigated in sham operated and nephrectomised animals for the same reason. Uraemia was induced by means of bilateral nephrectomy. The influence on solubility of main drug was investigated.

MATERIALS AND METHODS

Materials

Changes in percutaneous absorption were studied in diclofenac, ibuprofen and indomethacin, all purchased from Sigma Chemical Company (St. Louis, MO, USA). d-limonene which was used for its significant penetration enhancing effect was purchased from Tokyo Chemical Industries Co., Ltd. (Tokyo, Japan), as well as internal standard for HPLC assay, Octyl p-hydroxybenzoate. Urea and carboxyvinyl polymer, marketed as „HIVISWAKO 105 were supplied from Wako Pure Chemical Industries Ltd. (Tokyo, Japan). Other chemicals were of reagent or HPLC grade.

Gel ointments

The preparation of these formulations was published previously[7]. Our procedure was a modification of the above mentioned method. We used 2% concentration of main drugs and 1% of d-limonene. In case of formulations containing urea, the concentration corresponding to severe uraemia (50 mmol/l) and 10% as in topical formulations is used.

Animal procedures

Male Wistar rats weighing 170–190 g were used. The animals were taken to the experiment on the following day after bilateral nephrectomy. The BUN levels were estima-

ted using Urea Nitrogen-Test, Wako Pure Chemical Industries, Ltd. (Osaka, Japan), were between 40–60 mmol/l). After anaesthetisation with urethane saline solution (25%: 3 ml/kg i. p.) the rats were fixed on their back and the hair on their abdominal site of the body was removed with an electric animal clipper. Glass cells (16 mm inner diameter, 10 mm height) containing drug formulation under test (1.5 g) were attached to the shaved skin with cyanoacrylate type adhesives Aron Alpha A „Sankyo" (Toa Gosei Kagaku Kogyo Co., Ltd., Tokyo, Japan). Blood samples (250 ml) were collected via the jugular vein 2.5, 5, 7.5, and 10 h after the administration. Sham operated animals served as controls. Comparison of the elimination rate constants in the nephrectomised and sham operated rats employing elimination rate fraction Q_0 was performed to evaluate a possible direct impact on pharmacokinetics of studied drugs caused by the kidney loss.

$$Q_0 = K_{er} / k_N \qquad (\text{Dettli}^{8,9})$$

Q_0 is the elimination rate fraction in the anuric subject: it is identical with the fraction of the absorbed dose eliminated by extrarenal mechanism in subjects with normal kidney function, K_{er} is an extrarenal elimination rate constant, k_N elimination rate constant in healthy subject. The blood samples were collected via jugular vein at 10, 20, 40, 60 and 80 min after i.v. administration of ibuprofen (3 mg/kg) and indomethacin (1.5 mg/kg). Sampling times of diclofenac were 5, 10, 20 and 40 min after i. v. application of 3 mg/kg.

Determination of antirheumatics

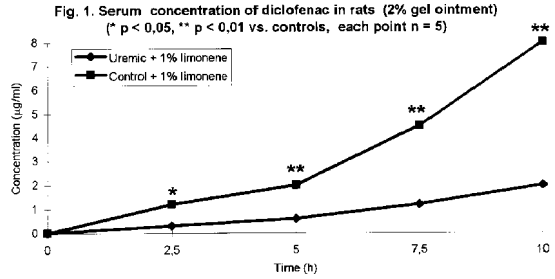
HPLC assay is described in the paper published by Okabe et al.[7]. HPLC Shimadzu LC-3A (Shimadzu Corporation, Kyoto, Japan) with ultraviolet detection at appropriate wavelength for each compound was employed. Column characteristics were 4.6 x 150 mm YMC Pack A-302 S-5 120 A ODS (Yamamura Chemical Laboratories, Co., Ltd., Kyoto, Japan). As a mobile phase mixture of 0.1% phosphoric acid and acetonitrile was used. The mixing ratio was adjusted according to the physical properties of each studied compound.

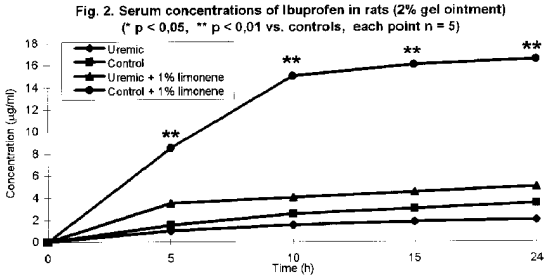
Determination of solubility of indomethacin

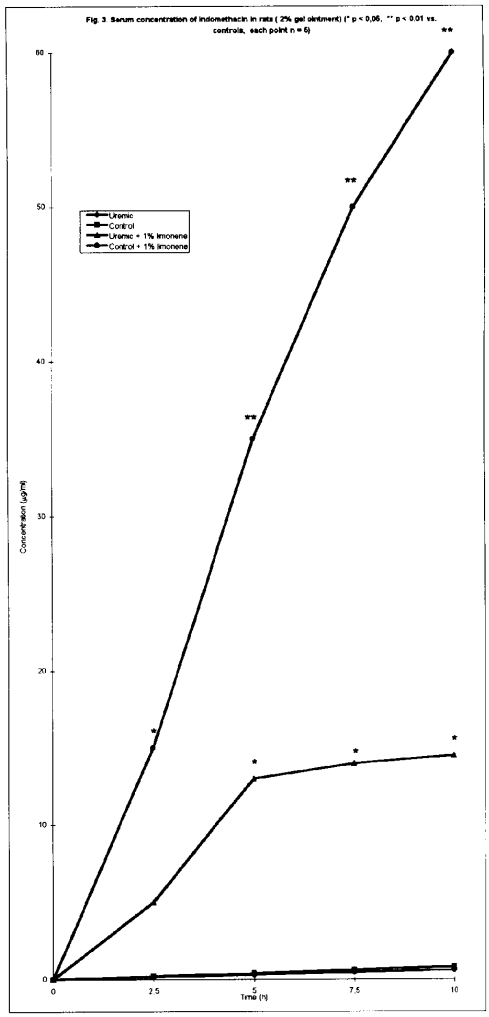
Indomethacin was selected as a model for other antirheumatics. An excess amount of indomethacin was added to the ethanol-water solution (50 : 50) and ethanol-water solution containing 10 % urea. After sonication, the solutions were kept at 37 °C for 48 hours. The concentration of indomethacin was estimated by means of UV/VIS spectrometer (Jasco U best-30, Japan Spectroscopic Co., Ltd., Tokyo, Japan) at 254 nm.

RESULTS

Three drugs (diclofenac, ibuprofen and indomethacin) eliminated entirely via nonrenal route were investigated. The results are summarised in Fig. 1–3. It can be seen that the transdermal absorption was significantly reduced in all three cases under the condition of experimentally induced uraemia when compared with the sham operated animals. The BUN concentration was in nephrectomised animals between 40 and 60 mmol/l, in the period of experiment (control BUN was 6 mmol/l during same period).

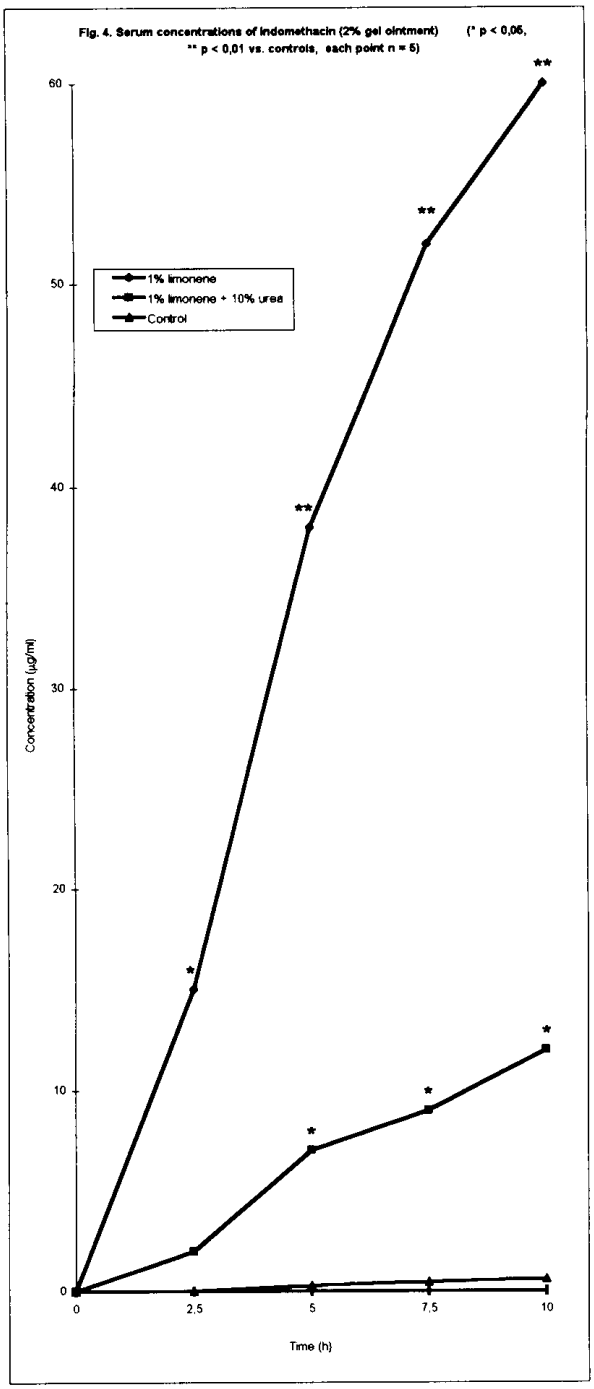






Further experiments were carried out to elucidate if the pharmacokinetics of studied drugs was altered to cause such decrease of transdermal absorption. For this reason the examination of elimination rate fraction Q_0 was performed. In all three cases the value of Q_0 was to 1.0 indicating that no changes in pharmacokinetics of investigated drugs after intravenous administration appeared.

As the behaviour of all three drugs was similar, further experiments were carried out only with indomethacin. In the first experiment, urea in concentration approximately 50 mmol/l was added to the gel ointment (corresponding with the mean BUN concentration in nephrectomised animals). The observed time-concentration profile of indomethacin was identical in both controls and with 50 mmol/l BUN concentration in formulation. Because urea can precipitate in the skin, the expected concentration should be much higher. Based on this experience and usual concentration of urea in pharmaceutical formulations, urea in 10% concentration was also used in gel ointment. In this case significant decrease in indomethacin serum concentration was observed (Fig. 4). To elucidate these changes solubility test was performed. A significant increase of solubility of indomethacin in the presence of 10% urea was observed. The ratio was 1: 2.5.



DISCUSSION

Because the changes in pharmacokinetic and pharmacodynamic behaviour of the drugs can influence their therapeutic value, our research was focused to elucidate if severe kidney damage caused by bilateral nephrectomy can influence the process of percutaneous absorption of drugs. Until now we have not found any reference dealing with possible changes of drug transport across the skin under any pathological condition, though many drugs were examined and found as possible candidate for percutaneous absorption e.g. levonorgestrel[10], azidothymidine[11], narcotic analgesics[12], or diclofenac[13]. To exclude direct effect of renal elimination, the selected drugs were eliminated extrarenally. The Q_0 examination confirmed that there is no effect on pharmacokinetics caused by kidney loss. On the other hand the transdermal absorption significantly decreased, which seems to have no relation to the elimination itself but may be associated with either metabolic or other changes due to uraemia. High BUN concentration is capable to increase urea concentration in the skin. This can be hardly clarified only by the experiments in which 10% urea was added to the gel ointment. The percutaneous absorption significantly decreased in relation to the increased solubility. There are at least two separate changes, one caused by overall changes due to uraemia and the other by the changes of physicochemical properties of the experimental formulation. The 50 mmol/l concentration corresponding to the BUN level in uraemic animals did not influence percutaneous absorption of healthy animals at all. It is difficult to examine the true concentration of urea in the skin of uraemic animals after 24 to 36 hours and the influence of this factor. The influence of surgical treatment was excluded using sham operated animals as controls and compared with normal animals, there were no differences between both groups. Our paper seems to be one of the first reports on this field of relationship between percutaneous absorption of the drugs and the uremic conditions of the organism. The results represent three drugs with the same behaviour. The diversity of physicochemical properties of each drug entity may carry out in the future contradictory results for each newly challenged drug for transdermal use, nevertheless these results indicate that the factor of disease should be considered.

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