

Ascorbic acid prevents cimetidine-induced decrease of serum hydrocortisone concentrations

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Introduction

Cimetidine (Tagamet®, Smith Kline & French, Rijswijk, the Netherlands) is a major histamine H₂ receptor antagonist. Intravenously, it has been advocated in critical and intensive-care medicine for the prevention of stress ulcers. Few side-effects of clinical importance, apart from gynaecomastia, have been reported [1]. Anti-androgenic effects of cimetidine have been reported [2]. Recently, it has been reported that cimetidine can decrease serum hydrocortisone concentrations in man [3].

Imidazoles, cimetidine, and etomidate (Hypnomidate®, Janssen, Beerse, Belgium), can bind to cytochrome P-450 at the active haem structure [4 5]. This causes a blockade of the cytochrome with a concomitant decrease of the serum hydrocortisone concentrations. Cytochrome P-450 proves to be essential for the 20-22 hydroxylation of cholesterol, the precursor for many steroid hormones [6]. Administration of cimetidine may result in low serum hydrocortisone concentrations. Intravenous administration of ascorbic acid is supposed to protect the serum hydrocortisone concentrations in patients whose steroid synthesis is inhibited by imidazoles [7]. The reason for this phenomenon is yet undetermined.

This prospective, blind, parallel study was designed to establish the effect of ascorbic acid on human hydrocortisone concentrations after cimetidine administration.

Methods

20 Consecutive male patients entered this study. Any patients suffering from renal, hepatic or endocrinological diseases and patients using

corticosteroid drugs, H₂ antagonists or any other imidazole including drug, in a period of four weeks prior to surgery, were excluded from the study population. Patients with incomplete data, because of short duration of surgery, were omitted. Patients receiving fresh frozen plasma were excluded from the study population. After exclusion for these criteria, 16 patients remained. These patients were randomly divided into two groups for a parallel-blind investigation.

All patients were scheduled for major abdominal vascular surgery lasting longer than 3.5 h. The study procedure and conditions were kept as uniform as possible. All procedures were scheduled for 08.00 and followed the same course during the morning. All patients needed invasive monitoring and intensive care postoperatively during 24 h. Informed consent was obtained from all patients the day before surgery and the study was in accordance with the standards of the hospital ethical committee, which bases its decisions on the Helsinki Declaration.

An epidural catheter was inserted between the third and fourth vertebra on the day prior to surgery. No premedication was given. Anaesthesia was induced with methohexital 1 mg/kg (Brietal®, Lilly, Nieuwegein, the Netherlands), piritramide 0.2 mg/kg (Dipidolor®, Janssen) and pancuronium bromide 1 mg/kg (Pavulon®, Organon, Oss, the Netherlands). Patients were ventilated throughout the surgical procedure. Bupivacaine 0.1 ml/kg (Marcaïne®, Astra, Rijswijk, the Netherlands) was administered via the epidural catheter at the time of induction. The radial artery and the subclavian vein were cannulated. This induction period lasted for approximately 20 min. The normal hydrocortisone profile of this

Keywords

Ascorbic acid
Cimetidine
Cytochrome P-450
Hydrocortisone
Metabolism
Steroid hydroxylases

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Boidin MP, Stuurman A, Erdmann W. Ascorbic acid prevents cimetidine-induced decrease of serum hydrocortisone concentrations. Pharm Weekbl [Sci] 1990;12(5):151-3.

Abstract

A blind, parallel, prospective, clinical study was conducted to investigate the effect of ascorbic acid on human serum hydrocortisone concentrations which were decreased by the administration of cimetidine. The study population included 16 male adults scheduled for major abdominal vascular surgery. The study was conducted in surgical patients under anaesthesia, in which steroidogenesis was inhibited by cimetidine. The results showed a reduction in serum hydrocortisone concentrations in patients receiving a placebo. In patients receiving ascorbic acid, there was a significant increase in serum hydrocortisone concentration. This reflects the normal serum hydrocortisone profile for this operation and anaesthetic technique. Cimetidine can bind to cytochrome P-450 covering the active haem group, the cytochrome proves to be of vital importance for hydroxylation reactions, involved in human steroidogenesis. Serum hydrocortisone concentrations will decrease when cytochrome P-450 becomes blocked. Intravenous administration of ascorbic acid was supposed to cause relief for this decrease. The reasons are undetermined yet. This investigation proved that ascorbic acid can prevent cimetidine-induced decrease of human serum hydrocortisone concentrations.

Accepted 7 June 1990.

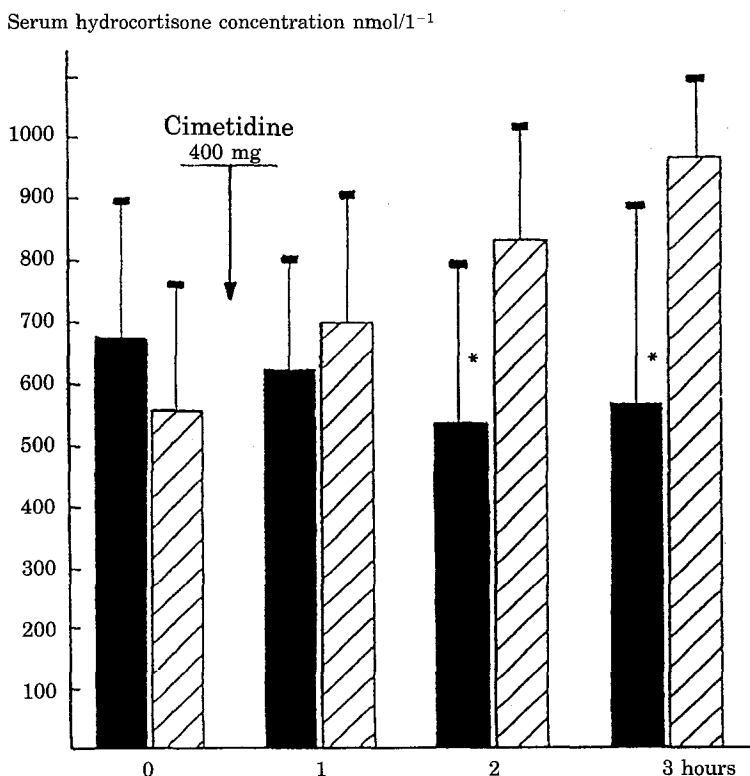
Table 1
Demographic data of the study population

Group	A	B	C
Drugs	cimetidine with placebo	cimetidine with ascorbic acid	control group
Patients	8	8	8
Age (years) (SD)	65 (8.1)	68 (9.1)	66 (7.3)
Weight (kg) (SD)	73 (9.1)	72 (9.6)	74 (9.3)
Surgery (h)	5.7 (4.2-7.3)	6.3 (5.2-8.2)	5.5 (4.5-6.6)
Blood loss (l)	1.7 (1.1-2.3)	1.9 (1.3-2.7)	2.1 (1.6-2.5)

anaesthetic technique is exactly known. The values of this historic control group, which were recorded in the same settings and in the same laboratories, were considered sufficiently reliable to serve as the control values for this study.

Physiological parameters, electrocardiogram, arterial systolic and diastolic blood pressures, central-venous mean pressure, heart rate, core temperature and urinary output, were monitored continuously. Blood, plasma expanders and electrolyte solutions for intravenous infusion, were administered as appropriate. Cloxacillin 1000 mg (Orbenin®, Beecham, Amstelveen, the Netherlands) was given intravenously to all patients, as a prophylactic antibiotic. No corticosteroid or any other drugs were given, except analgesics and muscle relaxants necessary for the maintenance of anaesthesia. Serum samples were taken before induction of anaesthesia and at 60, 120 and 180 min after cimetidine administration. All samples were immediately stored on ice, centrifuged and frozen as soon as possible. After collection of the samples, all patients received 1000 mg fresh ascorbic acid intravenously.

Figure 1
Serum hydrocortisone concentrations after placebo (group A: black) and after ascorbic acid (group B: shaded) administration. Steroidogenesis was inhibited by cimetidine (400 mg) in both groups. Mean and standard deviation.
*: $P < 0.01$



400 mg Of cimetidine was given as a slow intravenous bolus injection at the end of the induction of anaesthesia. In the contralateral arm a continuous drip infusion of 100 ml saline was started with either 10 ml of saline as a placebo (group A) or 10 ml fluid with 1000 mg of ascorbic acid (group B). The drip ran at twelve drops/min via an infusion pump (IVAC 300). This resulted in the administration of 100 ml fluid over 3 h. The administration code, registered in the hospital pharmacy department, could be obtained when necessary for clinical reasons.

Measurement of serum hydrocortisone concentration was made with the Coat-A-Count RIA Kit (Diagnostic Products Corporation, Los Angeles, USA). Within-run precision in the normal range (150-550 nmol/l) is 4%. Interassay precision in the same range is 8%. The least detectable level is 5 nmol/l. There is 65% cross-reactivity with prednisolone. Neither severe icterus, gross haemolysis, nor severe lipaemia have any effect on the procedure.

Mean values of samples taken at 60, 120 and 180 min in each group were compared with the pre-operative value. Statistical differences of the mean values were calculated with the one way analysis of variance [8].

Results

The two groups of 8 patients were comparable for demographic data (Table 1). Physiologic parameters in both groups showed no different mean values during anaesthesia. Arterial systolic, diastolic and mean pressures, central venous blood pressure, urine output and temperature showed essentially the same values in both groups. There were no major clinical differences between the two groups during the first 4 h of surgery.

In group A (placebo) there was a gradual decrease in serum hydrocortisone concentration. 3 Out of 8 patients reached levels beyond the low normal values. 7 Patients showed a decrease in serum hydrocortisone levels ranging from 0-60%. 1 Patient, however, showed a 30% increase in serum hydrocortisone concentration (Fig. 1).

In group B (ascorbic acid) there was a gradual increase of the serum hydrocortisone concentrations in the time. The increase is significant from the second hour until the end of the study period. All patients showed increased serum hydrocortisone levels ranging from 15 to just over 100%. Intergroup comparison demonstrated significant ($P < 0.001$) lower values in group A (placebo) when compared to group B (ascorbic acid).

Discussion

The moderate but significant increase in serum hydrocortisone concentrations is in accordance with the findings of Oyama and Takiguchi reporting on patients under spinal anaesthesia [9]. The normal hydrocortisone profile of this operation and anaesthetic technique in our hospital shows a slow but graduate increase of the serum hydrocortisone concentrations. The increase of the mean value proved to be from 56 nmol/l⁻¹ to 97 nmol/l⁻¹ after 3 h.

Administration of ascorbic acid appears to

have a protective effect on the serum hydrocortisone concentrations of patients who have received cimetidine intravenously. The reason for this phenomenon is not determined yet. The results of this study confirm the observations in previous studies. The serum hydrocortisone concentrations are comparable with the normal hydrocortisone profile for this operation and anaesthetic technique.

According to the manufacturer of cimetidine [Smith Kline & French, personal communication], no long-term animal studies have been performed to investigate the effects of cimetidine on serum hydrocortisone concentrations. Carlson and Ippoliti [10] found no negative effects on steroidogenesis in patients receiving cimetidine. Feely *et al.* [11] reported decreased levels of corticosteroid degradation products and aldosterone in the urine of patients receiving cimetidine. Kenyon *et al.* [12] published an *in vitro* study on the various effects of cimetidine and ranitidine (Zantac®, Glaxo, Nieuwegein, the Netherlands) in isolated bovine adrenal cells. Cimetidine concentrations greater than 200 µg/ml resulted in a 50% inhibition of hydrocortisone synthesis. With ranitidine, this effect only became apparent at 2000 µg/ml. De Natale *et al.* [13] suggested that bolus injections of cimetidine could temporarily suppress normal corticosteroid production. Recent evidence shows that cimetidine can block steroid synthesis in man [3]. In a double-blind study it was demonstrated that cimetidine decreased serum hydrocortisone concentrations. The same effect could not be demonstrated with ranitidine. This effect has only been observed in anaesthesia; probably because the feedback mechanism is blunted by the anaesthetic technique. Because of the anaesthetic technique, hydrocortisone is not increased by neurological stimuli caused by pain and surgical stress or awakeness.

It has been shown that ascorbic acid can restore the hydrocortisone synthesis in case of hypnomidate toxicity [14]. Also in the case of cimetidine toxicity there was a restoration of the serum hydrocortisone concentration after administration of ascorbic acid [3]. The mechanism is presently under investigation. Hornsby looked at the 11-beta-hydroxylase activity [15]. He suggested that ascorbic acid is a protective compound for cytochrome because 5 mM ascorbate prevented the rate of loss of 11-beta-hydroxylase activity in the presence of hydrocortisone. But no fitting explanation has been suggested at present.

The question remains as to whether or not these results have any clinical consequences. In the opinion of the authors it is highly probable that they have. Malnourished and postoperative patients, or patients for any reason treated solely

with dextrose or electrolyte-containing infusion fluids, run a high risk of catching an illness when cimetidine is prescribed. Without proper substitution of ascorbic acid the possibility exists that an acute Addisonian crisis may develop. Such a situation has been reported in the case of administration of etomidate [16].

Conclusions

Ascorbic acid appears to increase the serum hydrocortisone concentrations in patients under anaesthesia, when the steroidogenesis is inhibited by cimetidine. It is unclear from the presented data what the clinical implication will be for these patients.

Acknowledgements

The authors wish to thank Dr. R.A.E. Wirtz (vascular surgeon) for his kind permission to perform this study in patients primarily under his care.

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