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Pharmacokinetic characteristics and tolerability of a novel intravenous immunoglobulin preparation

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Abstract In two independent trials 10 and 12 healthy volunteers received the novel intravenous immunoglobulin (IVIG) preparations BT 511 and BT 507, respectively. BT 511 contains 5 g human plasma proteins per 100 ml, more than 95% of which are immunoglobulins of the G class (IgG). BT 507 contains in addition 61 IU antibody against hepatitis B surface antigen (anti-HBs) · ml^{-1}. In trial I volunteers received 4.0 ml/kg ($n = 4$) and 8.0 ml · kg^{-1} ($n = 6$) BT 511 to study the tolerability and the magnitude of the increase in immunoglobulins in plasma as well as their decline over 1 month. After administration of the lower dose, plasma IgG increased from 10.7 to 14.7 g · l^{-1} directly after the infusion. Following the 8.0 ml · kg^{-1} dose a more pronounced increase from 12.4 to 21.2 g · l^{-1} was observed. No adverse events occurred. After 1 month IgG concentrations had almost reached baseline values at 12.2 g · l^{-1} in the 4.0 ml · kg^{-1} group, but were still significantly increased at 15.2 g · l^{-1} after the high dose. There was a linear correlation between the maximal IgG plasma concentration and the subsequent decline of IgG during the 29-day observation period. After administration of BT 507 maximal anti-HBs concentrations of 1778 mU · ml^{-1} occurred 1.4 h after termination of the infusion. The terminal elimination half-life was 22.4 days, and total clearance and volume of distribution were determined to be 0.122 ml · min^{-1} and 5.41, respectively. The pharmacokinetic parameters calculated for anti-HBs as an indicator of IgG were in accordance with the pharmacokinetic behaviour of native IgG.

Key words Intravenous immunoglobulin G, Anti-hepatitis B; pharmacokinetic parameters, tolerability, healthy volunteers

Introduction

Intravenous immunoglobulin preparations (IVIG) are used for the treatment of congenital and acquired immunoglobulin deficiencies as well as for prophylaxis and treatment of viral diseases and severe sepsis [1].

The pharmaceutical production process of therapeutic immunoglobulin preparations derived from human plasma pools involves several steps, including fractionating according to Cohn et al. [2]. Enzymatic cleavage, chemical modifications or chromatographic steps are included in the production process in order to eliminate aggregates and increase the tolerability of these substances for patients [3, 4]. These modifications result in some alterations of the protein molecules and may therefore influence pharmacokinetic properties and antigen-neutralizing activity of the immunoglobulin molecules [3,5]. One important aspect of the immunoglobulins is that – due to their origin from human plasma – contamination is possible with pathogenic viruses such as HIV, HAV, HBV or HCV. The elimination of pathogens by the production process has to be proven by validated detection systems [6]. The most effective steps involve physical and chemical treatment such as wet heat, irradiation or a solvent-detergent method.

The aim of the trials presented here was to investigate the tolerability and the pharmacokinetic properties of the novel human immunoglobulin preparations BT 511 and BT 507, respectively (Biotest, Dreieich, Germany) in healthy volunteers.

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Methods

Both study protocols were approved by the local ethics committee and written informed consent was obtained from all participants. Inclusion criterion was the absence of any pathological findings at the baseline physical examination, which included 12-lead ECG, body temperature, blood pressure and heart rate measurements as well as measurement of clinical chemistry, haematology and coagulation parameters. Furthermore, all volunteers were screened for hepatitis A, B and C (anti-HBs, HBs-Ag, anti-HBc, anti-HAV, anti-HCV) and anti-HIV-1/-2.

Study medication

BT 511 and BT 507 were prepared only from plasma of test-negative donors (hepatitis A, B and C and HIV-1/-2) according to the German guidelines for blood transfusion. After Cohn's fractionation further steps included solvent/detergent treatment with octanoic acid, tri-*n*-butylphosphate and Tween 80; in addition chromatographic purification [high-performance liquid chromatography (HPLC)] was carried out using a cation exchange column. The validation of virus removal was carried out according to EC guidelines [6]. One hundred millilitres of BT 511/BT 507 contain 5 g human plasma proteins, of which more than 95% are 7S immunoglobulins of G class. The distribution of IgG subclasses is similar to those in natural IgG [7]; more than 90% of the IgG is present in the form of monomers and dimers, the content of aggregates being below 3%.

For the determination of the pharmacokinetic characteristics of IgG, an anti-HBs-enriched quantity of BT 507, containing 61 IU anti-HBs $\cdot$ ml^{-1}, was used. To produce BT 507, a defined amount of plasma from anti-HBs-positive donors (positive due to vaccination, free from anti-HBc and Hbs antigen) was included in the plasma pool, which was then further treated as for BT 511. Anti-HBs was chosen as a sensitive and easily measurable marker for IgGs [4], which is not produced by the volunteers, since other IgG antibodies, e.g. antibody against cytomegalovirus (anti-CMV), are likely to be found in the majority of the population.

Trial I

Ten healthy volunteers participated in the first trial, which investigated the tolerability of two different doses of BT 511, four of them receiving 4.0 ml $\cdot$ kg^{-1} body weight, the other six receiving 8.0 ml $\cdot$ kg^{-1} body weight. After an overnight fast volunteers came into the clinical department, where an indwelling cannula was introduced into a forearm vein. A blood sample was drawn for determination of safety laboratory and immunological parameters. Thereafter the infusion was started with 1.0 ml $\cdot$ min^{-1} and accelerated every 5 min up to 2.5 ml $\cdot$ min^{-1}. According to the different doses and body weights, the duration of infusion ranged between 2:12 and 3:01 h in the 4-ml $\cdot$ kg^{-1} group and between 4:05 and 4:52 h, in the group receiving 8 ml $\cdot$ kg^{-1} body weight. Blood samples were obtained directly after termination of the infusion, 24 and 48 h later as well as on day 29 after the infusion. Vital signs, i.e. blood pressure, heart rate and body temperature, were checked regularly during the infusion period and over the subsequent 24 h. Additional measurements were performed after 48 h and on day 29. On day 29 a final physical examination was carried out.

Safety laboratory parameters included clinical chemistry, haematology and coagulation parameters (i.e. partial thromboplastin time, prothrombin time, plasma fibrinogen concentration). In addition, immunological parameters – IgG, IgA, IgM and C3 and C4 complement factors – were determined. C3 and C4 complement factors served as simply detectable parameters providing information about complement activation due to aggregates or protease activities still remaining in the IVIG preparation.

Trial II

The second trial was performed in 12 healthy volunteers after baseline physical examination. As an additional inclusion criterion, they had to be anti-HBs negative. After an overnight fast, intravenous cannulas were placed into both forearms, one for the infusion of BT 507 and one for blood sampling. The infusion rate and stepwise increments were identical to those in trial I, the total volume of infusion was 100 ml and duration of the infusion was 49 (1) min. After the end of the infusion further blood samples for determination of anti-HBs levels were obtained at 1, 3, 6, 12 and 24 h (= day 2) as well as on days 3, 5, 8, 15, 22, 29, 43, 57, 71, 85 and 99. At each time point of blood sampling vital signs were measured.

Safety laboratory parameters identical to those in trial I were determined before and directly after the infusion, on days 2 and 99. Immunological parameters were evaluated on days 2, 3, 29, 71 and 99. The final examination on day 99 was performed according to the baseline examination.

Analytical measurements

Safety laboratory parameters were determined by routine methods; IgG, IgA, IgM and the complement factors were measured by nephelometry. Anti-HBs levels were analysed in duplicate by a sensitive solid-phase enzyme-linked immunoassay technique (AUSAB, Abbott, Germany). It has been demonstrated that this assay can detect anti-HBs in the presence of a variety of viral antibodies and antigens [8]. The intra-assay coefficient of variation was determined to 13% (n = 18), and the inter-assay variation coefficient was 11% (n = 18). The lower limit of detection was set at 10 mU/ml as instructed by the manufacturer.

Pharmacokinetic evaluation

For anti-HBs the pharmacokinetic parameters C_{max}, t_{max} and AUC as well as elimination half-life ($t_{1/2el}$), mean residence time (MRT), total clearance (CL) and volume of distribution (V_{ss}) were determined using the PC program TOPFIT [9]. Parameters were calculated according to both methods: compartment-free well as under the assumption of a two (or three-when appropriate) compartment model.

Statistical calculations

All pharmacokinetic and laboratory parameters are given as means with (SD) and statistical calculations were performed using the PC program SYSTAT. In both trials the following parameters were analysed by Wilcoxon's signed rank tests comparing the pre- and postinfusion values: concentrations of IgG, IgA, IgM and albumin as well as hematocrit. Spearman's correlation analysis was performed to determine (a) the dose-dependent increase in IgG, i.e. dose (ml $\cdot$ kg^{-1}) versus increase (g $\cdot$ l^{-1}) in IgG plasma concentration, and (b) the correlation between the maximal IgG concentration (C_{max}, g $\cdot$ l^{-1}) and subsequent decrease (Δg $\cdot$ l^{-1}) over the following 28 days.

Results

In both trials drug-related adverse events did not occur. Post-study tests for HBs-Ag, anti-HCV, anti-HBc and anti-HIV-1/-2 were negative in all participants. As BT

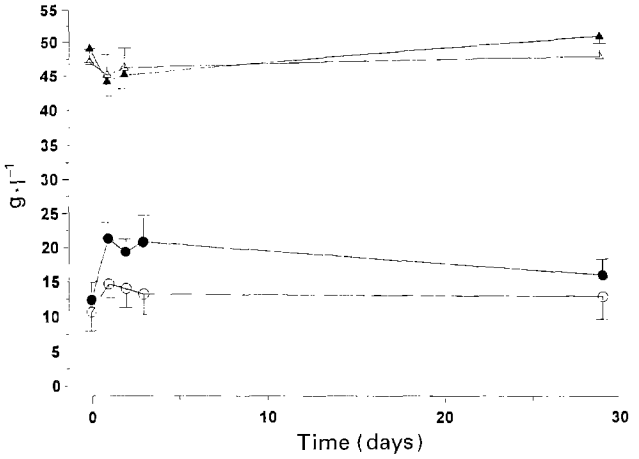

Fig. 1 Serum concentrations of IgG (*open circles* dose 4 ml · kg^{-1}, *closed circles* dose 8 ml · kg^{-1}) and albumin (*open triangles* dose 4 ml · kg^{-1}, *closed triangles* dose 8 ml · kg^{-1}) before and after the infusion of BT 511 in healthy volunteers (n = 4 received 4 ml · kg^{-1}, n = 6 received 8 ml/kg). Data are given as means with (SD)

511/507 also contains a considerable quantity of HAV antibodies, all subjects were test-positive for anti-HAV at their final examination.

Trial I

After administration of 4.0 ml · kg^{-1} BT 511 (n = 4), serum concentrations of IgG increased from a pre-treatment value of 10.7 (2.7) to 14.7 (2.0) g · l^{-1} directly after the infusion and decreased on the following day (Fig. 1, Table 1). With respect to IgM, IgA and albumin concentrations, marked changes did not occur (Table 1). Application of 8.0 ml/kg led to a more pronounced increase in IgG from 12.4 (2.3) g · l^{-1} to 21.2 (2.4) g · l^{-1} ($P < 0.05$) directly after the infusion and remained at this level on days 2 and 3 (Table 1, Fig. 1). Only in two subjects were maximal IgG concentrations observed directly after the infusion; in all other volunteers peak levels occurred on day 3. On average, there were no differences between plasma IgG concentrations between the time point directly after the infusion, and 1 and 2 days later. The increase in IgG ranged between 6.8 and 10.9 g · l^{-1}. On day 29 IgG levels at 15.2 (2.4) g · l^{-1} were still significantly ($P < 0.05$) elevated when compared to pre-infusion values. IgM and IgA levels remained almost unchanged throughout the study. Albumin concentrations fell significantly ($P < 0.05$) after the infusion and returned to baseline values on day 2 (Fig. 1, Table 1). Serum complement factors, coagulation parameters and clinical chemistry data showed no clinically relevant changes during the study. For hematocrit and albumin a significant decrease ($P < 0.05$) was observed post-infusion for both groups. On day 2 pre-treatment values were regained (Table 1). A linear correlation was observed between maximal IgG concentrations and the decrease in IgG concentrations during the subsequent 28 days (r = 0.778, $P < 0.01$, Fig. 2).

Trial II

Maximal anti-HBs concentrations at 1778 (204) mU · ml^{-1} were measured 1.4 (1.2) h after termination of the infusion (Fig. 3). The model-independently calculated AUC came to 29.74 (5.75) U · ml^{-1} · day, and the elimination half-life was determined to be 22.4 (4.2) days. Total clearance was calculated to be 0.122 (0.028) ml · min^{-1} and the mean residence time to be 31.9 (5.9) days. The average volume of distribution was 5.4 (0.8) l. With the exception of one subject, anti-HBs concentration/time curves could be described by a two-compartment model, and in one case a three-compartment model proved to be more appropriate according to the Akaike criterion. Model-derived data were in good agreement with the above-mentioned parameters and are given in Table 2. Even after infusion of the smaller volume of 100 ml (between 1.0 and

Table 1 Immunoglobulin and albumin concentrations and haematocrit values before and after the infusion of BT 511 (trial I) ND = not determined

	IgG (g · l^{-1})	IgA (g · l^{-1})	IgM (g · l^{-1})	Albumin (g · l^{-1})	Haematocrit (%)
Dose 4 ml · kg^{-1} (n = 4)					
Before	10.7 (2.7)	2.48 (0.28)	1.67 (0.54)	47 (2)	45.4 (2.1)
After	14.7 (2.0)	2.46 (0.28)	1.63 (0.57)	45 (3)	43.6 (2.3)**
Day 2	14.0 (2.7)	2.42 (0.32)	1.60 (0.54)	46 (3)	45.5 (2.8)
Day 3	13.2 (2.9)	2.78 (0.35)	1.64 (0.51)	ND	ND
Day 29	12.2 (3.2)	2.67 (0.46)	1.83 (0.52)	47 (2)	46.7 (2.9)
Dose 8 ml · kg^{-1} (n = 6)					
Before	12.4 (2.3)	2.06 (0.71)	1.40 (0.87)	49 (2)	45.1 (2.8)
After	21.2 (2.4)*	2.29 (0.88)	1.51 (0.92)	44 (2)*	43.1 (3.8)**
Day 2	19.3 (1.8)*	2.20 (0.76)	1.24 (0.91)	45 (2)*	45.0 (2.4)
Day 3	20.7 (4.0)*	2.56 (0.88)	1.64 (1.08)	ND	ND
Day 29	15.2 (2.4)*	2.32 (0.88)	1.59 (0.8)	50 (1)	47.1 (2.5)

* $P < 0.05$
** $P < 0.05$, both groups were analysed together

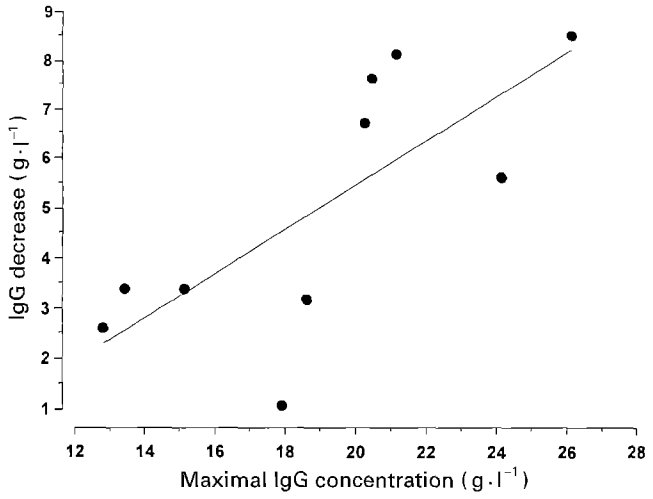

Fig. 2 Correlation between maximal IgG concentration (in $g \cdot l^{-1}$) and the subsequent decrease in IgG concentrations over the subsequent 28 days (Spearman's $r = 0.778$, $P < 0.01$)

1.6 $ml \cdot kg^{-1}$), albumin concentrations decreased significantly (Table 3). As in trial I, infusion of BT 507 did not influence clinical chemistry, coagulation parameters and complement factors. IgM and IgA serum levels were not markedly altered during the course of the study. IgG concentrations rose from 10.9 (2.6) to 12.0 (2.3) $g \cdot l^{-1}$ after the infusion and to 12.3 (2.6) $g \cdot l^{-1}$ on day 3 (Table 2; $P < 0.05$). Using data from both trials, a linear dose/response relationship could be shown between the dosage of IgG given (over the dose range from 1.0 to 8.0 $ml \cdot kg^{-1}$) and the maximal IgG serum concentration measured ($r = 0.939$, $P < 0.001$).

Discussion

The novel IVIG preparation BT 511, as well as BT 507, was well tolerated in all subjects with respect to clinical status, blood chemistry, haematology and coagulation parameters. Since C3 and C4 complement factors were not influenced, the presence of relevant levels of IgG aggregates or remaining proteases in the preparations used seems to be unlikely [5]. The infusion of 8.0 $ml \cdot kg^{-1}$ BT 511 resulted in a significant decrease in blood cell counts and albumin concentration, suggesting a dilution effect due to the high infusion volume up to 690 ml. In addition, maximal IgG concentrations occurred in some volunteers with a delay of 2 days after the high dose and the anti-HBs maximum was measured on average 1.4 h after termination of the infusion. Similar observations were reported by Hagenbeek et al. [10] after an i.v. infusion of an anti-CMV IgG preparation in bone marrow transplant recipients, where anti-CMW peak concentrations occurred at 24–48 h after administration. Following an i.v. dose of anti-HBs IgG, Shibata et al. [11] measured maximal anti-HBs 1 h after administration. These findings may be explained by diffusion of IgG molecules into the extravascular space during the infusion period and subsequent distribution processes thereafter [11, 12]. Unfortunately, we did not measure IgG concentrations or anti-HBs during the infusion and we may have missed an earlier peak. Pharmacokinetic model analysis confirmed the superiority of a two-compartment model, possibly reflecting an initial distribution phase [11, 12], and a terminal elimination half-life, reflecting the catabolism of the IgG [13]. The calculated volume of distribution for anti-HBs at 5.41 was slightly lower than the value of 6.391 reported by Glöckner [14]. Investigations with ^{125}I-labelled IgG have shown that only 45% of the IgG remains in the intravascular space; the remaining 55% may escape via the capillaries and diffuse into the tissues [8, 11, 12, 15]. However, the calculated central compartment with a volume of distribution of 2.91 may represent the distribution of IgG in the plasma volume [13].

Over the IgG dose range from 1.0 ml/kg (trial I) to 8 $ml \cdot kg^{-1}$ (trial II) a linear correlation between the dose of IgG administered and the increase in IgG plasma concentrations was observed. In addition, a linear correlation also exists between the maximal IgG serum concentration and the amount eliminated during the 29-day observation period, supporting earlier findings, where a concentration-dependent catabolism of IgGs has been postulated [4, 15, 16].

An essential property of IgG preparations is the biological half-life of the antibody molecules, which can be determined using radioactively labelled immunoglobulins [4, 5, 15] or specific IgG antibodies [3, 10, 11, 17–20]. Both methods have their shortcomings; the measured radioactivity does not warrant the integrity of the molecule and requires additional confirmation by other test methods [5]. On the other hand, antibody measurements may not precisely represent total IgG metabolism [13] and antibodies may not be evenly distributed between the four IgG subclasses [7]. Furthermore, Fab fragments of anitbodies are more rapidly catabolized and eliminated than intact molecules [7]. The analytical method applied measured intact molecules and we therefore determined the pharmacokinetic parameters of intact IgG. The calculated half-life for anti-HBs of 22 days is in accordance with the half-life of native IgG [7, 13]. Comparable half-lives of 21.7 (5.4) days after i.v. administration of anti-HBs IgG and 24.1 (5.7) days after i.m. administration were

Table 2 Pharmacokinetic parameters of anti-HBs calculated according to a two-compartment model ($n = 11$) or a three-compartment model ($n = 1$)

	AUC ($U \cdot ml^{-1} \cdot day$)	$t_{1/2el}$ (days)	CL ($ml \cdot min^{-1}$)	V_c (l)	V_{ss} (l)	MRT (days)
Mean	28.87	22.1	0.130	2.9	5.4	30.7
SD	5.64	3.7	0.034	0.2	0.7	5.9
Min	17.1	17.6	0.094	2.6	4.4	23.7
Max	36.4	30.2	0.193	3.3	7.1	39.9

Table 3 Immunoglobulin and albumin concentrations and haematocrit values before and after infusion of 100 ml BT 507 ($n = 12$) ND = not determined

	IgG ($g \cdot l^{-1}$)	IgA ($g \cdot l^{-1}$)	IgM ($g \cdot l^{-1}$)	Albumin ($g \cdot l^{-1}$)	Haematocrit (%)
Before	10.9 (2.6)	2.01 (0.70)	1.28 (0.87)	47 (2)	45.7 (2.9)
After	12.0 (2.3)	1.93 (0.62)	1.03 (0.39)	46 (3)	45.1 (3.5)
Day 2	12.1 (2.1)*	2.03 (0.69)	1.11 (0.40)	48 (3)	46.1 (3.1)
Day 3	12.3 (2.6)*	2.06 (0.75)	1.14 (0.38)	ND	ND
Day 29	11.4 (2.7)	2.13 (0.87)	1.18 (0.45)	ND	ND
Day 71	11.5 (2.7)	2.36 (0.95)	1.29 (0.48)	ND	ND
Day 99	11.5 (2.6)	2.20 (0.82)	1.23 (0.46)	49 (3)	46.7 (2.8)

* $P < 0.05$

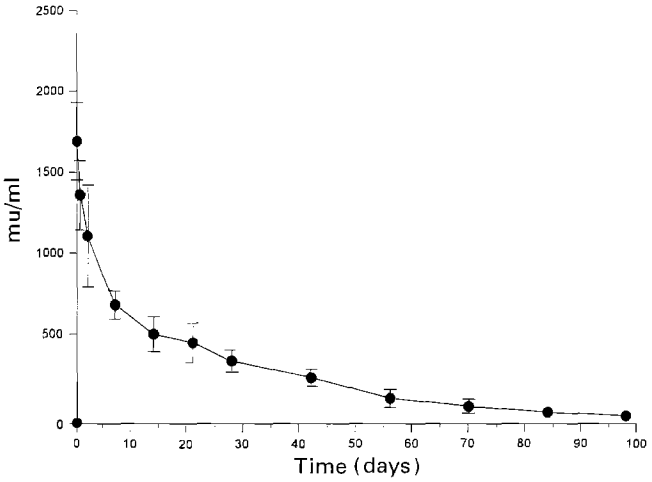

Fig. 3 Anti-HBs serum concentration/time profile after the infusion of 100 ml BT 507 (containing 61 mU/ml) in 12 healthy volunteers. Data are given as means with (SD)

reported by Glöckner [14]. For anti-CMV-enriched IgG average half-lives between 20 days [18, 20] and up to 96 days [17] were determined in patients following bone marrow transplantation. Markedly shorter half-lives of 30–70 h for anti-CMV have been reported by Hagenbeek et al. [10] after administration of a 7S IVIG preparation in bone marrow recipents. These observed discrepancies underline the fact that the half-life of IgG is influenced by the disease state [5, 7, 20, 21] and the actual serum concentration [5, 16], as our own data from trial I show. Therefore, data obtained in healthy volunteers and those from patients should be compared cautiously. The pharmacokinetic characteristics of IgG – independent of the health state of the recipient – are determined by the integrity of the molecule. The proven similarity between the half-life of anti-HBs in BT 507/511 and the half-life of native IgG suggests that the production process does not impair biological characteristics, i.e. biological half-life, antigen-binding activity of IgG, in this preparation. However, the pharmacodynamic properties of the immunoglobulins administered were not further evaluated in our trials.

In conclusion, the novel IVIG preparations BT 511 and BT 507 were well tolerated in healthy volunteers, and seroconversion with regard to HBV, HCV and HIV-1/2 did not occur in any of the volunteers. The pharmacokinetic characteristics of anti-HBs, measured as a representative of immunoglobulins of the G class, are in accordance with results previously published. Moreover, the close agreement of the calculated half-life for anti-HBs with the half-life of human native IgG suggests an almost completely preserved integrity of the immunoglobulin molecules, which is necessary for the biological function of IgGs.

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