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Sundhedsudvalget
SUU alm. del - Bilag 15
Offentligt

ZLB Behring

København den 8. februar 2005

Som reaktion på de seneste dages omtale af ZLB Behring ApS og leveringen af Sandoglobulin (frysetørret og flydende) i dagspressen:

Sagsforløb:

Frem til og med 2003 har Statens Serum Institut haft monopol på forarbejdning af dansk blodplasma.

På baggrund af en påtale fra EU er dette monopol ophævet, således at forarbejdning af blodplasma og efterfølgende indkøb af blodprodukter nu sker via offentlig licitation.

Den første licitationsrunde blev iværksat i 2003.

ZLB Behring ApS (herefter ZLBB) vandt denne licitationsrunde foran Statens Serum Institut og Octapharma, og har dermed eneret til at forarbejde dansk blodplasma til blodprodukter for Danmark frem til 31. august 2007.

ZLBB og Amgros I/S underskrev den 24. november 2003 en kontrakt om indkøb af lægemidler (immunglobulin og albumin) fremstillet ud fra dansk plasma.

ZLBB begyndte i henhold til kontrakten primo januar 2004 at indsamle blodplasma fra de danske blodbanker.

ZLBB kunne i henhold til kontrakten primo september 2004 levere frysetørret Sandoglobulin og flydende Albumin til de danske sygehuse.

ZLBB har i det oprindelige tilbud til Amgros – og senere i kontrakten med Amgros angivet en forventet tidshorisont for lanceringen af flydende Sandoglobulin til januar 2005. På grund af forsinkelse i registreringsproceduren i England vil det først være muligt at levere flydende Sandoglobulin fra maj/juni 2005. Dette er allerede i sensommeren 2004 kommunikeret af ZLBB til Amgros og herfra videre til sygehusene.

Vedrørende sikkerhed:

Samtlige immunglobulin præparater registreret i Danmark bærer en identisk advarsel vedrørende risikoen for nedsat nyrefunktion og nyresvigt. Dette gælder også Octapharmas flydende præparat, som pt. anvendes på Rigshospitalets intensivafdeling.

Der er ikke påvist en sammenhæng mellem indholdet af stabiliseringsstoffer (f. eks. sucrose eller maltose) i immunglobulin og forekomsten af nedsat nyrefunktion og nyresvigt (se i øvrigt for flere detaljer det vedhæftede "Safety of Sucrose-Stabilized IVIG in Diabetic and Nephropathy Patients"). Ligeledes er der ikke påvist en forskel i risikoen for nedsat nyrefunktion eller nyresvigt for frysetørrede immunglobuliner henholdsvis flydende immunglobuliner.

Tilfælde af nyresvigt ved brugen af immunglobuliner til risikopatienter er meget sjældne.

ZLB Behring

Sandoglobulin er – ligesom alle andre lægemidler – under løbende kontrol af Lægemiddelstyrelsen (jf. notits på Lægemiddelstyrelsens hjemmeside 4. februar 2005).

Vedrørende Blodforsyningsloven:

Tapning af dansk blod må i Danmark kun ske fra frivillige, ubetalte donorer og må kun iværksættes af blodbanker tilknyttet det offentlige sygehusvæsen.

Det kan være svært at tilsikre, at blodplasma fra udlandet er tappet fra ubetalte frivillige donorer.

Et centralt princip i blodforsyningsloven er, at Danmark, for så vidt det er muligt, skal være selvforsynende af blod og blodprodukter.

ZLBB er den eneste virksomhed, som leverer albumin og immunglobulin baseret på dansk blodplasma. Anvendelsen af andre blodprodukter (baseret på blodplasma fra udenlandske donorer) strider således mod intentionerne i Blodforsyningsloven.

Omtale vedrørende Statens Serum Institut (SSI):

Det blodplasma som tidligere var indsamlet af SSI (i 2002 og 2003) levede ikke op til de nye sikkerhedskrav (PCR-tests), som var specificeret i licitationsmaterialet fra Amgros. ZLBB kunne derfor ikke anvende dette plasma.

Det er derfor ikke korrekt, at ZLBB skulle overtage 73 ton blodplasma fra SSI, idet dette blodplasma ikke levede op til de nye sikkerhedskrav.

ZLB Behring:

ZLB Behring er en af verdens førende producenter af plasmaprodukter og vores produktionsfaciliteter i Bern, Schweiz, er nogle af de mest højteknologiske.

Der anvendes årligt ca. 230.000 gram immunglobulin i Danmark. Sandoglobulin er til dato anvendt af mere end 3 millioner patienter på verdensplan, som tilsammen har modtaget over 100 millioner gram Sandoglobulin – svarende til Danmarks samlede forbrug i over 400 år.

Sandoglobulin og Albumin "ZLB" er i Danmark udelukkende baseret på blodplasma doneret af frivillige, ubetalte danske donorer og tappet hos de danske blodbanker.

Morten Svenningsen
adm. direktør
ZLB Behring ApS

Safety of Sucrose-Stabilized IVIG in Diabetic and Nephropathy Patients

Data Supporting the Safety of Sucrose

In more than 20 years of clinical use of our product which is marketed worldwide under the names Sandoglobulin, Panglobulin, Sanglopor, Redimune and Carimune, over 100 million grams of IVIG products have been administered to more than 3 million patients worldwide. ZLB's IVIG products maintain an excellent safety record.

Renal dysfunction is rarely reported

Renal dysfunction and acute renal failure have been reported in a small number of IVIG recipients, almost exclusively in those with pre-existing renal complications. Typical for this side effect are increased serum creatinine and blood urea nitrogen (BUN) concentrations, which become evident one to several days after the infusion. In the majority of affected patients renal function return to baseline spontaneously within a few days after discontinuation of IVIG treatment, and no further complications are seen. Occasionally, however, especially after several infusions on consecutive days, oliguria or anuria may develop, resulting in the need for dialysis.

In 1999, FDA requested that manufacturers of all IVIG products, marketed in the USA, included a warning statement in their product information. In this warning statement ("Black Box") special risk situations/patients at risk are defined. *Patients predisposed to acute renal failure include patients with (1) any degree of pre-existing renal insufficiency, (2) diabetes mellitus, (3) age greater than 65, (4) volume depletion, (5) sepsis, (6) paraproteinemia, or (7) patients receiving known nephrotoxic drugs.*

Based on reports received by the ZLB pharmacovigilance department between 1998 and November 2004, acute renal failure was identified approximately once in 20,000-30,000 infusions, which corresponds to one episode in 5,000-10,000 patients. According to the definition used by CIOMS Working Groups III and V (1), such a frequency is considered to be a rare event.

Public health impact is negligible

It is important to note that among IVIG recipients, death is rarely due to renal failure. Most of the rare cases of IVIG-associated renal failure cases have had a benign outcome. Even in these cases, artifacts and confounding effects may explain many of the reports. Associated predisposing clinical conditions have been identified. It is particularly significant that IVIG solutions containing higher sucrose concentrations (9% and 12 % solutions) are not associated with any increase in the reported rate of renal failure.

Interpretation of data

It has been suggested that the nephrotoxicity of IVIG preparations is due to an osmotic injury to the proximal renal tubules caused by sucrose in several brands of IVIG (2). However, there are also case reports of renal failure in patients receiving IVIG without sucrose, but containing maltose, glycine or glucose as inhibitors of IgG aggregation. Formal proof of a causative role for IVIG in renal impairment is lacking, and the exact role of sucrose remains unclear. Thus IVIG itself may be contributing to or causing renal damage.

More than 50% of cases with acute renal failure, reported to the FDA, were ITP patients with high dose treatment of 0.4-0.8g/kg body weight on several consecutive days. On the other hand, patients with primary immune deficiencies, who were typically treated with lower doses, were rarely affected (3).

A possible explanation for the higher frequency of renal adverse events with sucrose containing IVIG products is their preferential use in high risk patients and in patients requiring high dose treatment: Sucrose containing IVIG are used preferentially in hospitalized patients, while for out patient use, non sucrose containing are often preferred (Sucrose containing IVIGs are lyophilized. For out patient use, ready for use liquid preparations are considered more convenient.) Sucrose containing IVIG may also be used preferentially in diabetic patients, as no adjustment of glucose supply or insulin dosage is required, in contrast to glucose or maltose containing products,. A large proportion of patients with adverse event reports of renal dysfunction had concomitant diabetes.

Renal toxicity associated with other carbohydrate stabilizers

It should be noted that all carbohydrates presently used as stabilizers in IVIG solutions (maltose, etc) show a potential to effect mechanisms of acute renal insufficiency of the type associated with IVIG. These include tubular obstruction secondary to carbohydrate-induced nephropathy, ischemia secondary to renal artery vasoconstriction and abnormal glomerular hemodynamics due to increased plasma osmotic pressure. It should also be considered that reports of renal dysfunction may be disproportionately higher in patients receiving higher dose IVIG regimens, regardless of the stabilizer used. This effect may be due to the deposition of immune complexes in the glomerulum or interstitium (4). The presence of other confounding variables in these patients makes interpretation of such data extremely difficult. It cannot be excluded that some of the effects could be consistent with a causative role of high protein concentrations and/or a rapid infusion rate.

Recommendations given in the P.I.

Predisposing factors associated with reports of renal dysfunction with IVIG treatment include dehydration, pre-existing renal insufficiency (creatinine $\geq$1.5 mg/dl), age > 65 years, underlying paraproteinemia or rheumatoid factor and diabetes mellitus. Accordingly, these predisposing factors are mentioned in the product labeling as precautions.

Conclusion

No change in favourable risk-benefit ratio

It must be recognized that IVIGs are generally used in seriously / critically ill patients. There has been an uninterrupted excellent overall safety record of Sandoglobulin during at least the last 20 years of worldwide use. During this period, renal dysfunction and complications of diabetes have been rarely reported. Such cases as do exist have almost always had favorable outcomes.

How to reduce the risk

The risk of acute renal failure can be minimized by adequate hydration of patients with pre-existing renal impairment prior to infusion, by reconstitution of IVIG to a solution with low protein concentration and osmolality, ie, a 3% solution, as well as by a slow infusion rate, not exceeding 2 mg IgG/kg body weight per minute. In patients with the aforementioned risk factors, serum creatinine and urinary volume should be monitored during treatment and for at least 3 days after the administration of IVIG.

In summary, in pre-disposed patients a careful risk-benefit evaluation should be undertaken. This risk-benefit assessment should be done with **any IVIG brand** irrespective of the stabilizing additives. To our current knowledge, the exact role of stabilizing sugars in causing renal complications is not clear. The oncotic effect of the macromolecular immunoglobulin itself may induce complications (5). Thus, the minimal possible dose, concentration and infusion rate should be administered in patients at risk of acute renal failure.

Literature

1) Report of CIOMS Working Group III and V (Guidelines for Preparing Core Clinical-Safety Information on Drugs, Geneva, 1999).
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4) Barton JC, Herrera GA, Galla JH, Bertoli LF, Work J, Koopman WJ. Acute cryoglobulinemic renal failure after intravenous infusion of gamma globulin. Am J Med. 1987 Mar 23;82(3 Spec No):624-9.
5) van Zanten A.R.H., Beekhuyzen M, van der Meer Y.G., de Gooijer A., Feith G.W. (2003) [Acute renal failure following treatment with intravenousimmunoglobulins] Acuut nierfalen na behandeling met intraveneus toegediende immunoglobulinen. Ned.Tijdschr.Geneeskd.147 (7):307-310.