

Impact of manufacturing improvements on clinical safety of albumin: Australian pharmacovigilance data for 1988–2005

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After more than six decades of use, human plasma-derived albumin remains an important clinical therapy. Presenting as an iso-oncotic or hyperoncotic preparation, albumin is an effective plasma volume expander or albumin replacement solution in a number of indications, including hypovolaemia and shock due to haemorrhage, trauma, sepsis and hypo-proteinaemia in acutely ill patients.

Concerns about the safety of albumin have historically focused on viral safety, hypotensive reactions and mortality. Human albumin solutions have had an excellent viral safety record worldwide since their introduction, due to the incorporation of a pasteurisation procedure for viral inactivation.¹ Adverse drug reactions (ADRs) to albumin solutions are now generally uncommon, mild and transient. However, ADRs to early generation albumin solutions were more commonly associated with impurities in the final product, such as aggregates and prekallikrein activator (PKA).² The latter has been implicated as a cause of hypotensive reactions,²⁻⁴ one of the more frequently reported ADRs to albumin. PKA indirectly activates kininogen to form bradykinin, a potent vasodilator.⁴

Mortality associated with albumin administration has been closely scrutinised and debated since the publication of a meta-analysis from the Cochrane Injuries Group Albumin Reviewers (1998) which claimed an increase in mortality in patients treated with albumin.⁵ While the Cochrane methodology, particularly trial selection and patient numbers, has been debated, it should also be noted that the studies involved albumin products manufactured more than a decade ago. The findings of the Cochrane study have been challenged by the recent publication of a large, multicentre, randomised double-blind trial (the SAFE study), which demonstrated no difference in mortality between the critically ill patient group receiving albumin and the group receiving saline as the resuscitation fluid.⁶ Reassessment by the Cochrane Injuries Group in 2004⁷ was followed by the issue of updated safety alerts from both the United States Food and Drug Administration⁸ and Health Canada,⁹ which stated that concerns raised by the initial Cochrane report had been resolved.

Long-term post-market surveillance of spontaneously reported ADRs can provide a valuable insight into safety trends in large populations over time. Recently, two retrospective studies of spontaneous post-market pharmacovigi-

ABSTRACT

Objective: To evaluate the impact of manufacturing improvements on the clinical safety of human albumin solutions in Australia.

Methods: This retrospective study examined the incidence of spontaneously reported post-market adverse drug reactions (ADRs) in Australia associated with successive generations of albumin products manufactured by the Bioplasma Division of CSL Limited (CSL Bioplasma) over 18 years (1988–2005). Key characteristics of each product generation which could affect clinical safety, such as purity, aggregates and prekallikrein activator (PKA) levels, were also identified from CSL batch release records.

Results: A total of 3.7 million bottles of iso-oncotic and hyperoncotic albumin products were distributed in Australia over the period. Improvements to manufacturing processes resulted in products with increased albumin purity, lower levels of impurities such as aggregates and PKA, and reduced batch-to-batch variation. The total ADR incidence (number of ADRs per 100 000 bottles distributed) associated with the products currently supplied was 1.5 and 1.7 for Albumex 4 (2VI) and Albumex 20 (2VI), respectively. This was a significant reduction compared with the earlier generation products Stable Plasma Protein Solution (14.1) and 20% Normal Serum Albumin (11.5), respectively ($P < 0.0001$). In particular, hypotensive reactions declined substantially.

Conclusion: Post-market pharmacovigilance data collected for successive generations of human albumin products supplied in Australia over 18 years indicates that manufacturing improvements have significantly improved the clinical safety profile of this product.

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lance data collected by albumin manufacturers have been published,^{10,11} but neither included the products manufactured in Australia, which are supplied only to the Asia Pacific region as part of national self-sufficiency arrangements.

The Bioplasma Division of CSL Limited (CSL Bioplasma) is the national fractionator and sole supplier of albumin solutions in Australia. A number of manufacturing improvements have been implemented over the years, and post-market

Table 1. History of albumin products produced by CSL Bioplasma

Product	Years of distribution	Manufacturing method	Viral inactivation steps
Iso-oncotic			
Stable Plasma Protein Solution (SPPS)	1963–1991	Cohn fractionation	Pasteurisation
5% Normal Serum Albumin (NSA)	1992–1995	Cohn fractionation	Pasteurisation
Albumex 4/5 (1VI)	1995–2000	Cohn + chromatography	Pasteurisation
Albumex 4 (2VI)*	2000–present	Chromatography	Pasteurisation + low pH incubation
Hyperoncotic			
20% Normal Serum Albumin (NSA)	1989–1995	Cohn fractionation	Pasteurisation
Albumex 20 (1VI)	1995–2000	Cohn + chromatography	Pasteurisation
Albumex 20 (2VI)*	2000–present	Chromatography	Pasteurisation + low pH incubation

* Albumex 2VI products manufactured by CSL Bioplasma are supplied under the tradename NSA in Hong Kong, Malaysia and Singapore. VI = viral inactivation.

pharmacovigilance data have been collected in parallel. The aim of this study was to examine the impact of manufacturing changes on the clinical safety profile of the albumin products used in Australia between 1988 and 2005.

Methods

This was a retrospective study of Australian post-market pharmacovigilance data for the years 1988 and 2005.

Manufacturing processes

CSL Bioplasma's albumin products are manufactured from voluntarily donated blood and plasma collected by national blood services. Since the 1960s, there have been four distinct generations of iso-oncotic albumin preparations and three generations of hyperoncotic products supplied for clinical use (Table 1).

The first iso-oncotic product was Stable Plasma Protein Solution (SPPS). This sterile 5% plasma protein solution was manufactured by the Cohn ethanol-fractionation process and contained about 86% albumin and 14% α - and β -globulins. In 1992, SPPS was superseded by 5% (w/v) Normal Serum Albumin (NSA), which was prepared by an improved Cohn method and had an albumin purity > 96%. The improvements involved changes in pH and ethanol concentrations at fractionation steps to ensure increased albumin purity. A hyperoncotic product, 20% NSA, was also developed.

From 1995, Albumex 1VI (single viral inactivation) iso-oncotic and hyperoncotic products were manufactured by a combination of Cohn fractionation and chromatography. The crude albumin fraction generated by Cohn fractionation was further purified chromatographically using two ion exchange steps and one gel filtration step. Viruses were inactivated by pasteurisation, as for the earlier products.

The subsequent and current generation of products, Albumex 2VI (two viral inactivation steps), is purified by chromatography alone, using defibrinated plasma as the starting material. The chromatographic procedure is identical to that used in the Albumex 1VI product. A low pH procedure is incorporated into the manufacturing process in addition to pasteurisation to enhance virus inactivation.

Batch analysis data

The levels of purity, aggregates and PKA in albumin release batches were measured at CSL Bioplasma using British Pharmacopoeia methods.¹² The sample sizes available for the different batches of albumin products were: SPPS, 401 (albumin purity and aggregate content) and 415 (PKA); 5% NSA, 251 (purity) and 248 (aggregate content and PKA); Albumex 4/5 (1VI), 175 (all variables); Albumex 4 (2VI), 110 (all variables); 20% NSA, 73 (purity), 66 (aggregate content) and 54 (PKA); Albumex 20 (1VI), 57 (all variables); and Albumex 20 (2VI), 57 (all variables).

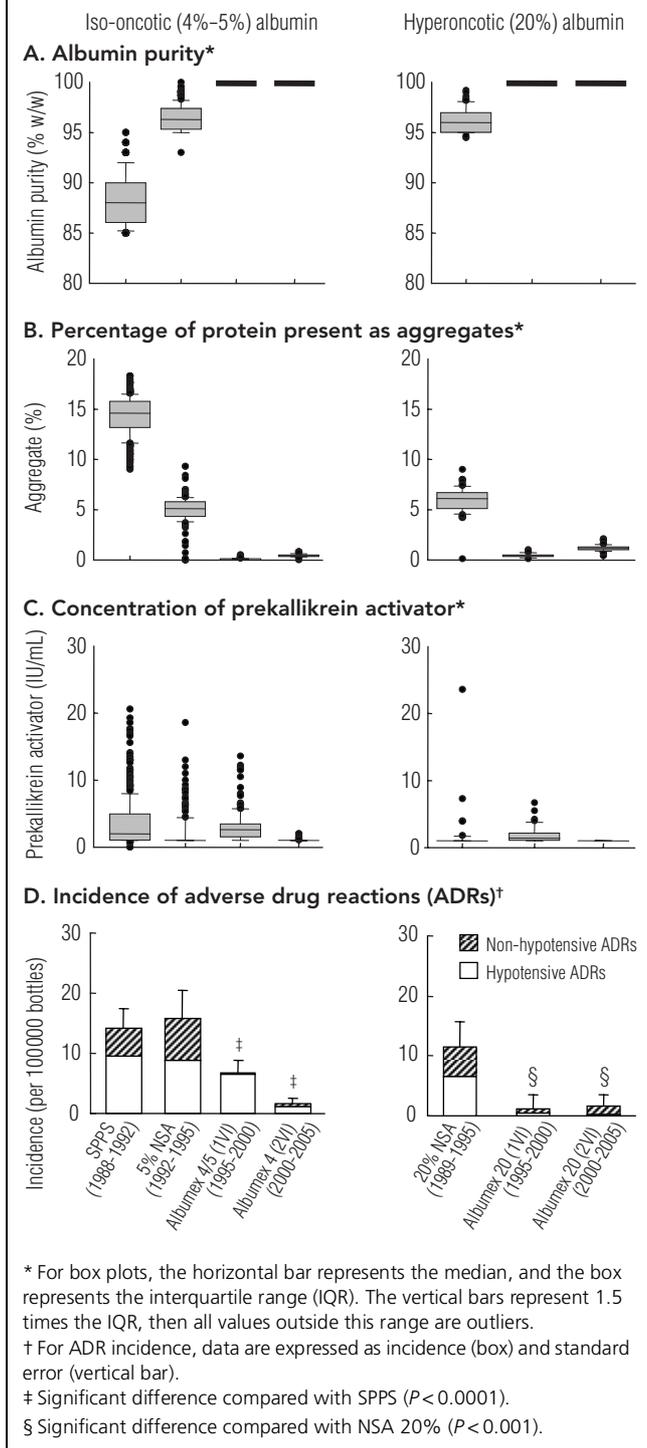
Adverse drug reactions

All Australian ADRs spontaneously reported to CSL Bioplasma between 1988 and 2005 were included in the study. ADRs were classified as hypotensive (reports containing the words or terms "hypotension", "hypotensive", "fall in blood pressure", "blood pressure fell" or "blood pressure dropped") or non-hypotensive (reports without these terms). A search was also conducted to identify any cases of suspected viral transmission or where death was reported as an outcome.

Product usage data

Information on the prescription of albumin at the patient level was not available, and thus calculation of individual patient exposure was not possible. As a surrogate measure,

Figure 1. Characteristics of successive generations of albumin preparations and incidence of adverse drug reactions in Australia



the number of bottles of albumin distributed in Australia was used as the denominator to calculate ADR reporting incidence.

Statistical analysis

The levels of purity, aggregates and PKA in each product group were graphed as box plots using SigmaPlot 9.0 (Systat Software Inc, Calif, USA). The ADR incidence was expressed as the number of ADR reports received per 100 000 bottles of product distributed. Statistical analysis was performed using Intercooled Stata 9.1 (StataCorp, College Station, Tex, USA). Maximum likelihood estimates of ADR incidence and Clopper–Pearson 95% confidence intervals¹³ of these incidence statistics were calculated. The *P* values reported for a difference between two estimates of ADR incidence were calculated using Fisher’s exact test. Albumex 4/5 and Albumex 20 products were compared with the first generation products (SPPS and 20% NSA, respectively). The level of significance was adjusted for multiple comparisons according to the Bonferroni principle.¹⁴

Results

Process improvements

Process improvements resulted in a marked increase in albumin purity from about 88% for SPPS to greater than 99% for Albumex 1VI and 2VI (Figure 1A). There was also a decrease in the presence of aggregated material. In SPPS and NSA, about 14% and 5%, respectively, of protein content was in the form of aggregates, whereas in the Albumex products, aggregates accounted for less than 2% (Figure 1B). PKA levels also decreased with successive product generations. In particular, a notable decrease was observed for Albumex 2VI, where 90% of batches had PKA levels ≤ 1 IU/mL (Figure 1C). The change to the Albumex generation of products was also associated with a reduction in batch-to-batch variation of albumin purity, aggregates and PKA levels (Figures 1A–1C).

Adverse drug reactions

About 2.7 million bottles of iso-oncotic albumin preparations and 1 million bottles of hyperoncotic preparations were distributed in Australia between 1988 and 2005. The incidence of total, hypotensive and non-hypotensive ADRs reported per 100 000 bottles distributed is shown in Figure 1D.

Overall, the Albumex 1VI and 2VI preparations had significantly lower incidences of all ADRs and of hypotensive ADRs than the earlier generation products, with the exception of Albumex 4 (1VI). For the latter, hypotensive ADRs accounted for 99% of reported ADRs, the highest ratio among all products examined. These cases included a cluster of 20 reports received between March and August 2000, 18 of which involved the administration of bovine-derived gelatin-based plasma volume expanders (Gelifu-

sine [B Braun] and Haemaccel [AFT Pharmaceuticals]) before Albumex 4 (1VI).

The incidence of non-hypotensive ADRs also decreased significantly for Albumex 4/5 (1VI and 2VI) compared with SPPS. A similar trend, although not reaching significance, was seen for Albumex 20 (1VI and 2VI) in comparison with 20% NSA. The non-hypotensive ADRs reported for earlier generation products were most commonly shivering/rigors, increased temperature and nausea, whereas the few ADRs reported for the Albumex products involved primarily skin rashes.

Mortality

Death was notified as an outcome in two ADR reports, both of which involved earlier generation products. In one case, a 77-year-old man received SPPS during a surgical procedure. He developed irreversible hypotension and disseminated intravascular coagulation and subsequently died. The other death was of an 81-year-old man who received 20% NSA during treatment for multiple trauma and developed bronchospasm and cardiac arrest.

Virus transmission

There were no cases of suspected viral infection reported to CSL Bioplasma associated with any of the albumin products.

Discussion

This comparison of successive generations of albumin products manufactured by CSL Bioplasma between 1988 and 2005 highlights a significant reduction in the incidence of spontaneously reported ADRs, especially hypotension, which paralleled improvements in product purity.

Historically, concern about the hypotensive effect of the first-generation product SPPS was initially expressed by two groups of Australian clinicians. They noted that fast infusion of SPPS induced a fall in systolic and diastolic blood pressure in patients on cardiac bypass during cardiopulmonary operations¹⁵ and in patients undergoing therapeutic plasmapheresis.¹⁶ The presence of PKA in albumin solutions was later suggested to cause the "hypotensive syndrome".² Other uncharacterised vasoactive impurities have also been implicated.¹⁷ At the time, it was decided to monitor all albumin batches and to release only batches with a PKA level less than 20% of the International Reference Preparation (ie, 35IU/mL) for clinical use.

The change from the SPPS to the NSA generation of albumin products through modification of the Cohn fractionation process increased albumin purity and decreased aggregate and PKA content. However, no significant improvement in clinical tolerability was observed. Either the

reduction in impurities was not sufficient to have an impact, or possibly other activated components remained which had the capacity to elicit adverse reactions.

A significant decrease in ADR incidence was achieved only with the introduction of Albumex, with albumin purity increasing to >99%, and a further reduction in aggregates and PKA levels. This suggests that the chromatographic process increases product purity and removes residual proteins responsible for triggering adverse reactions. In particular, it has been shown that the size-exclusion chromatography step using a Sephacryl S200 column (GE, Uppsala, Sweden) is effective in removing high molecular weight impurities and PKA-related complexes.¹⁷ The removal of PKA or precursor complexes during purification is essential for obtaining a low PKA product as PKA inactivation during pasteurisation can vary.¹⁸ Albumex 4/5 (1VI) was the only product in the Albumex product group that did not show a significant decrease in the incidence of hypotensive ADRs. This may have been due to a cluster of cases reported between March and August 2000. Investigation of these cases showed that there had been co-administration of one of the synthetic plasma volume expanders Gelofusine or Haemaccel just before Albumex 4 (1VI), which confounded assignment of the cause of the ADR. At the time, Gelofusine had only recently been introduced to the Australian market, and its potential for hypotensive reactions was less known.¹⁹ In addition, just before the cluster reporting period, some Haemaccel batches were recalled in response to a high number of hypotensive reactions, possibly caused by the presence of vasoactive substances which directly activate the kinin pathway.²⁰ These gelatin-based plasma volume expanders may therefore have contributed to some of the hypotensive ADRs that were assigned to albumin.

The change from Albumex 1VI to Albumex 2VI resulted in a further decrease in PKA to levels almost unmeasurable in most batches. It is possible that the introduction of the prolonged incubation step at low pH may have been responsible for further inactivation of PKA²¹ and other vasoactive substances.¹⁷ This may account for the significant reduction in ADRs, especially hypotension, in this generation of products.

This study was based on spontaneous post-market pharmacovigilance data, which are generally recognised to underestimate the actual incidence of ADRs. However, Australia has one of the highest per capita reporting rates in the world,²² together with a close surveillance network by the Australian Red Cross Blood Service, which was an advantage for this study. Furthermore, the Cochrane review in 1998, which claimed an excess mortality among albumin recipients, attracted worldwide attention and heightened awareness of albumin safety.⁵ In Australia, this led to the

SAFE study⁶ in 2001 using Albumex 4 (2VI), which subsequently allayed concerns about mortality.

CSL Bioplasma has always been the sole manufacturer and supplier of human albumin products in Australia. Almost all ADR reports provided the trade name and/or batches involved. The company was therefore in a unique position to monitor the impact of manufacturing changes on the clinical safety of its albumin products. This study indicates that improvements in the manufacturing technology of CSL Bioplasma's albumin solutions have resulted in high purity products with an excellent record of clinical safety. In particular, hypotensive reactions, which were historically a relatively common event for these types of products, are now rare with the chromatographically purified products currently available in the Asia Pacific region.

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