

ORIGINAL PAPER

Presence of medication taken by blood donors in plasma for transfusion

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Vox Sanguinis

Background and Objectives The TRIP national hemovigilance and biovigilance office receives reports on side-effects and incidents associated with transfusion of labile blood products. Anaphylactic reactions accounted for the largest number of serious transfusion reactions in the period 2008–2012. In most cases, no cause is found for these reactions. TRIP data show that anaphylactic reactions occur relatively frequently with transfusion of plasma or platelet concentrates. Data from blood services show that 10% or more of plasma donors regularly use medication which is permitted under donation guidelines. It is conceivable that medication taken by the donor in plasma for transfusion could cause an anaphylactic transfusion reaction in the recipient. This exploratory study investigated the presence of drugs or drug metabolites in donor plasma.

Materials and Methods Samples (5 ml) were taken from thawed, quarantine fresh frozen plasma units (FFP) which had to be rejected for transfusion because of leaks or length of time after thawing. The samples were analysed for approximately 1000 drugs and drug metabolites using a toxicological screening method.

Results Eighty-seven samples were analysed. Toxicological screening was positive in fourteen samples (16%). In eleven samples, one substance was found, and in three samples, the presence of two or three drugs was detected.

Conclusion After freezing, storage and thawing of fresh FFP, it is possible to detect medication taken by the donor. Further investigation is recommended to analyse whether donors' medication in plasma can be implicated in some cases of allergic or anaphylactic reactions in transfusion recipients.

Key words: allergy, anaphylactic transfusion reaction, donor medication, hemovigilance, plasma.

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Introduction

The Dutch national hemovigilance and biovigilance office TRIP (transfusion and transplantation reactions in patients) registers reports on side-effects and incidents associated with the transfusion of labile blood products in the Dutch hospitals. The category of anaphylactic reac-

tion, defined as allergic reactions with systemic features such as stridor, dyspnoea, fall in blood pressure, vomiting or diarrhoea, accounted for the largest number of serious transfusion reactions in the period 2008–2012. In most cases, no cause is found for anaphylactic transfusion reactions. TRIP data show that anaphylactic reactions are more frequently associated with the transfusion of plasma or platelet concentrate (PC) than with transfusion of red blood cell concentrate (RBC) [1]. The relatively high incidence of anaphylactic reactions associated with the transfusion of PC may be due to the plasma which is present

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in the PC. Data from blood services show that at least 10% of plasma donors regularly use medication which is permitted under donation guidelines [2, 3]. It is conceivable that medication taken by the donor, or its metabolites in plasma for transfusion, could cause an anaphylactic transfusion reaction in a recipient [4, 5]. Pharmacological effects in patients transfused with plasma containing medication which is permitted under donor guidelines are considered unlikely. This exploratory study investigated the presence of drugs or drug metabolites in quarantine fresh frozen plasma units (FFP) after quarantine, storage and thawing.

Materials and methods

In the Netherlands, FFP units are prepared from plasma collected by apheresis from volunteer donors by the national blood service, Sanquin; the procedure yields products which contain $<5 \times 10^6$ leucocytes per unit and in 90% of units $<1 \times 10^6$. Units are frozen within 24 h of collection and stored at -25°C or lower. They are released and distributed to hospitals after the donor has been retested for infectious disease markers after the prescribed quarantine period (6 months). According to standard international guidelines, donors are screened using a health questionnaire which includes questions to ascertain regular medication as well as short-term use of medicines since their last attendance. Use of painkillers <4 days before donation is specifically elicited. Donors are deferred for donation while on or following recent use of medication which entails a donor or a recipient hazard.

During 2011 and 2012, staff of the laboratory of the transfusion service of the HagaZiekenhuis, a large teaching hospital in The Hague in the Netherlands, collected samples of 5 ml from thawed FFP units which had to be rejected for transfusion because of leaks or length of time after thawing, with a target of 100 samples. Up until screening, the samples were stored frozen again at -70°C .

Only samples for which the blood supply organization confirmed that the donor had consented to anonymous research use were included. The samples were analysed in the pharmacy, Apotheek Haagse Ziekenhuizen, (Central Pharmacy for The Hague Hospitals) for approximately 1000 drugs and drug metabolites using a toxicological screening method which has been described elsewhere [6, 7]. In brief: an alkaline buffer and internal standard are added to 0.5 ml of plasma. Organic solvent is then added, and samples are vortex mixed. Samples are centrifuged, and the organic layer is separated and evaporated. The residue is dissolved in 40 μl mobile phase, and 20 μl is injected into a high-performance liquid chromatography (HPLC)-diode array analytical system. The chromatographic system is connected to a library comprising over 1000 drugs and metabolites. Peaks are identified and quantified based on retention and spectrum. This procedure isolates alkaline and neutral drugs. The same procedure is repeated with an acidic buffer to isolate acidic drugs. The limit of detection for each compound is equal to or lower than the usual lowest therapeutic concentration. All samples which contained detectable substances were considered as positive.

In order to assess whether findings could be representative of the Dutch donor population, we downloaded data on the top prescribed medicines in the Netherlands for 2010 and 2011 (www.gipdatabank.nl), [8, 9]. The expectation was that the detectable drugs would belong to the most frequently used drugs and, because donors are relatively healthy people, that over-the-counter (OTC) drugs would be present. The list of drugs found in the FFP units was compared to the top 25 and the top 100. A search in PubMed was performed for all the substances that were found in the toxicological screening, to find out if severe allergic and/or anaphylactic reactions had been described in literature. Also the Farmacotherapeutisch Kompas (FTK), a kind of physicians' desktop reference to pharmacotherapeutics, was consulted in order to find information

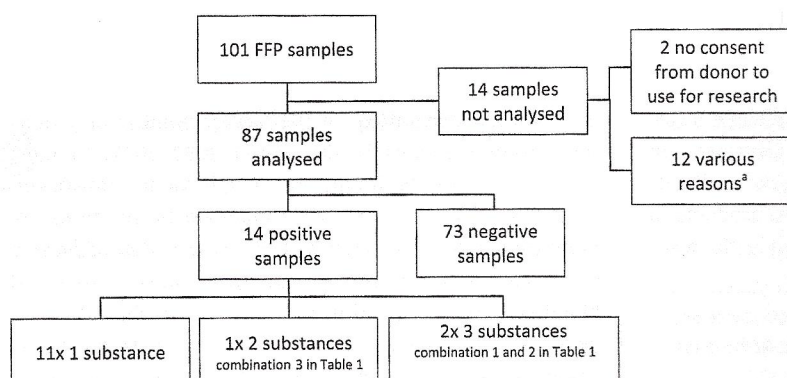


Fig. 1 Results of toxicological screening.

^aFor example, two samples were erroneously taken from pooled SD-plasma, one frozen plasma units (FFP) unit was sampled twice and for other samples, the unit identification number (EIN) was not listed or the pharmacy did not receive the sample.

Table 1 Substances found in frozen plasma units (FFP)

Type of drug/substance	Name	Total no. of positive samples ^a	Found in combination ^b	Anaphylactic reaction described in publication	Occurrence of anaphylactic reaction according to FTK	No. of possible anaphylactic reactions reported to Lareb
Non-steroidal anti-inflammatory	Naproxen ^c [10, 11]	4	C3	Y	Rare (<0.1%)	50
Antihypertensive	Valsartan	2		—	—	3
	Telmisartan	3	C2	—	Rare (<0.1%)	1
	Amlodipine	1	C2	—	Very rare (<0.01%)	3
	Metoprolol	1	C2	—	—	9
Proton pump inhibitor	Omeprazole ^c [14]	1		Y	Rare (<0.1%)	16
Psychopharmaca	Paroxetine	1		—	Very rare (<0.01%)	9
	Citalopram [15, 16]	1	C1	Y	% not yet known (but reported)	6
	Pipamperone	1	C1	—	—	—
	Quetiapine	1	C1	—	Sometimes (<1%)	2
Oral antidiabetic	Glicazide	1		—	—	—
Anabolic steroid	Metenolone	1	C3	—	—	—
Preservative	Methylparaben [12, 13]	1		Y	—	—

FTK, Farmacotherapeutisch Kompas; Lareb, Netherlands Pharmacovigilance Centre.

^aIncluding the samples in which a combination of substances was found.

^bIn one FFP, the mentioned drug was found in combination (C) with the drugs indicated by the same number.

^cPrescription and over-the-counter (OTC) drug in the Netherlands.

about anaphylactic reactions to the drugs that were detected. Finally, the database on the website of the Netherlands Pharmacovigilance Centre Lareb (<http://www.lareb.nl>) was searched for numbers of reported possible anaphylactic reactions to these drugs.

Results

The laboratory collected 101 samples of which 87 samples could be analysed (Fig. 1). Toxicological screening was positive in 14 samples (16%). Table 1 shows an overview of the substances that were found and summarizes the search results regarding anaphylactic reactions [10–16]. In eleven samples, only one substance was determined, in one sample two, and in two samples, three drugs were detected.

Twelve different drugs and one preservative were recognized. The concentrations found did not exceed the concentrations expected under normal use of that particular medicine. The drugs detected in 11 out of the 14 positive samples (78%) were among the top 100 of prescribed drugs. Five of the drugs that were found (metoprolol, omeprazole, amlodipine, paroxetine and citalopram) belong to the top 25 of most prescribed drugs in 2010 and/or 2011 in the Netherlands. According to the literature and information from the FTK at least eight of the found substances are capable of causing an anaphylactic reaction in a sensitized person.

Discussion

This exploratory study shows that it is possible to detect medication taken by a plasma donor after freezing, quarantine and thawing of the FFP. A blood service internal pilot study (J. Wiersum, personal communication 2013) established that some 10–20% of donors regularly take prescribed or OTC medication. In 16% of the analysed units of FFP substances were measured using toxicological screening, which is in line with this finding. Except for metenolone, an anabolic steroid which is illegal in the Netherlands, all the detected medicines are permitted under donation guidelines. Because donors are relatively healthy people, we expected to find drugs which are widely used and which are frequently used for minor health problems or to prevent future health problems, such as analgesics, antihypertensive drugs or drugs to lower the blood cholesterol concentration. The drugs detected in 11 out of the 14 positive samples (78%) were among the top 100 of prescribed drugs. An unexpected but interesting finding was that of methylparaben, a substance that is used as a preservative (E218), but also occurs naturally for example in blueberries. According to literature, parabens can cause anaphylactic reactions [12, 13]. The most frequently found drug, naproxen, is an OTC drug that is only eligible for reimbursement by health insurance under certain conditions. This probably explains why naproxen does not show up in the top 25

of most prescribed medicines. At least eight of the detected substances are capable of causing anaphylactic reactions according to the literature and information from the FTK. Despite the dilution that occurs when a unit is transfused into a patient, FFP containing a pharmaceutical substance could cause an anaphylactic reaction in a sensitized recipient since very small quantities of allergen may suffice. Pharmacological effects in patients transfused with FFP units containing these types of medicine seem very unlikely because of the dilution that occurs in the circulation of the recipient.

Allergic/anaphylactic reactions (ATRs) account for a large number/proportion of serious transfusion reactions. Allergy is a hypersensitivity reaction typically mediated through immunoglobulin (Ig)E. IgE will bind to the surface of mast cells and basophils, after which mediators such as histamine, leukotrienes and cytokines are released. Donor and recipient as well as product factors have been shown to play a role in some ATRs. However, despite recent work examining donor, recipient and product factors in ATRs, the causative mechanisms for the majority of the ATRs remain elusive [17]. The most obvious way in which medication could cause an ATR is if it is an allergen for a sensitized patient. Alternatively, according to literature, non-steroidal anti-inflammatory drugs (NSAIDs) like naproxen can also cause non-allergic anaphylaxis due to spontaneous mast cell degranulation which leads to histamine release [18–21]. This means that even without prior sensitization an anaphylactic reaction can occur in response to NSAIDs. It is not clear whether this process depends on the plasma concentration of the NSAID and what the effect of dilution with transfusion will be. Because naproxen was also the most frequently found medication in the tested FFP units, a possible role of NSAIDs should be investigated further in relation to anaphylactic reactions.

This is a small exploratory study. To the authors' knowledge, it has not hitherto been specifically demonstrated that donor medication can still be detected in plasma after freezing and storage for several months. Although the possibility of allergic reactions in sensitized patients being triggered by medication taken by a blood donor has been suggested, the authors are not aware of work supporting their possible role in transfused patients without prior sensitization. Although the units for sampling were not selected using a specific randomisation procedure, the sampling procedure had the effect of randomization since the occurrence of leaks in a bag or patient care-related reasons for a unit not being used within the time limit after thawing are

not linked to donor medical history or possible medication use. It is possible that more units contained traces of pharmaceutical substances but that these were below the detection thresholds of the analytical method. Because the limit of detection of the analytical method for each compound in the library is below or equal to the lower end of the range of therapeutic concentrations, regularly used medication is detected and incidental use might be missed. However, the results are in line with the expectations.

Based on the present findings, we recommend further work to elucidate a possible role of medication in donated blood in ATRs. Additional information about patient characteristics including known allergies to medication or other substances could be analysed. On the donor side, a look-back for information about medicines taken at the time of donation, combined with an alert about a recipient ATR in the records of associated donors, could provide more insight in the relation between medication in plasma and such reactions. Donor investigations have been proposed in the Netherlands, but are not currently routine. If a relation between donor medication and ATRs is found, this could lead to specific blood component selection (e.g. use of platelets conserved with additive solution or concentrating platelets and/or plasma donor selection or washing of cellular blood components) for patients with a history of allergic or anaphylactic reactions to blood transfusion or in other settings. It could also lead to restrictions on donation in relation to use of certain drugs. However, if a change to acceptance criteria were proposed, such that no medication was permitted, this would have a significant impact on sufficiency of the donor base.

Conclusion

In this pilot study, it was possible to detect pharmaceutical substances taken by the donor in thawed quarantine FFP. The findings show that some anaphylactic transfusion reactions could conceivably be explained by the presence of prescribed or OTC drugs in FFP transfused to a sensitized or even a non-allergic recipient. Further research on allergic transfusion reactions and the possible relation to presence of medication in donated blood is recommended.

Conflict of interest

AT, DT and MS none, JW is also employed by the national blood service Sanquin.

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