THE SWISS EXPERIENCE OF HAEMOVIGILANCE

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Introduction and history

Switzerland is a small country with a population of about 7.2 Mio and an area of 41'285 km2. The gross domestic product per capita is about 27'500 USD. Switzerland is member of the Council of Europe, but not of the European Union. Switzerland consists of 26 political independent districts ("Kantone"). In the 5 major cities the universities have a medical faculty with an university hospital, every "Kanton" has one larger hospital and several smaller regional hospitals; this sums up to a total of 585 hospitals (1:12'500 inhabitant). Health insurance is mandatory and about 20 % have a private insurance which allows a free choice of the hospital and physician in Switzerland. The costs for the health system are high.

On 13.6.1951 Swiss Red Cross received by a decree of parliament the acknowledgement and responsibility for the blood transfusion service for civil and military purposes. No other organisation than Swiss Red Cross was active in blood banking. On 22.3.1996 a new decree for the control of blood, blood products and transplants with implementation of Good Manufacturing Practice principles was released and since 1.1.2002 the New Federal Health Law is in force. According to this legislation blood products are handled equivalent to drugs.

In 1974 the Blood Transfusion Service of Swiss Red Cross was founded as a non-profit organisation with voluntary and non-remunerated blood donation. In the 80s, before the HIV era, the Blood Transfusion Services of Swiss Red Cross (BTSSRC) was an association of 15 large transfusion centers and 45 small transfusion services at hospital sites. The foundation of the Central Laboratory ZLB was the organisation with the largest activities in blood banking. ZLB and BTSSRC agreed on common recommendations on donor selection, blood products, laboratory analysis and quality control, but these recommendations had voluntary character with no legal power for compliance. In 1994, the Parliament asked for an analysis of the HIV crisis in the late 80s. The main conclusion was, that it seemed necessary to build a new transfusion service organisation with clear responsibilities, no uncertainties, no delays and with concentration and specialisation in their activities. The over 60 blood transfusion services of different size were reduced to 13 regional blood transfusion services (mostly foundations) with one leading centre performing all activities. The smaller hospital sites were reduced in number and activities (only donor selection, blood donation, no production or testing activities). On 4.12.99 a new association consisting of these 13 BTS and the Swiss Red Cross as 14th member was established. All 13 regional BTS are non-profit organisations with no public subsidies, with a total full-time staff of about 550 and a turnover per year of approximately 70-80 Mio USD. Today, clear guidelines exist for all activities in blood transfusion, from donor selection, preparation, apheresis, product specifications, product codes, analysis, reagents, materials, look back. The quality guidelines are referenced in the guidelines of the Council of Europe and the PIC/S guidelines. Of these 13 BTS 3 are ISO-certified and 3 have an accreditation EN 17025 (former EN 45001). In the eighties whole blood was replaced by buffy-coat depleted Red Blood Cells (RBC). Nowadays the following blood products are used: leucodepleted packed red cells, platelets from buffy-coat or apheresis (PT) and fresh frozen plasma (FFP). Since 1.9.1999 general leucodepletion is mandatory because of its well-known advantages, but eventually triggered by the fears of vCJD. 80% of the blood is produced by whole blood filtration, 20% by component filtration, in centres with a need of buffy-coat for platelet production. Since 1993 Fresh Frozen Plasma has to be virus-inactivated (1993-2000

with methylenblue, after 2000 with Solvent/Detergent) or quarantine stored (donor retested after 4 month). The following tests are performed on each donation : Anti-HIV 1/2/0, Anti-HCV, HBsAg, Syphilis, ALAT, AB0/Rhesus, since 1.7.1999 HCV NAT and since 1.3.2002 NAT testing for HIV.

See table 1 for blood donation and use of blood products

Haemovigilance

In Switzerland haemovigilance started in a somewhat special way. An obligation for immediate notification of serious adverse events to the authorities existed, but experiences in the past in monitoring adverse events following vaccinations showed that cooperation between physicians and government was minimal. Therefore, in January 1996 the Blood Transfusion Service of Swiss Red Cross (BTSSRC) launched in collaboration with the Swiss Drug Monitoring Centre (SANZ) a spontaneous reporting scheme, called Haemovigilance. The idea to work together with the private foundation of SANZ was to profit from a well established reporting system which included an information system and reporting forms and to profit from the experiences and knowledge in analysing adverse drug reactions in pharmocovigilance and last, but not least, to be independent and accepted by physicians. With all these advantages it was possible to set up the system in very short time, even before the law concerning blood, blood products and transplants was implemented on 1st August 1996. The scheme was run by a single physician in a part-time. In the same year a second reporting scheme for viral transmission and epidemiologic survey was assigned to the reference laboratory of BTSSRC. Primarily the Central Laboratory (ZLB) in Berne was responsible, but after the ZLB was sold to an Australian company the blood transfusion part was separated from the pharmaceutical part of the plant. Therefore, the task of the reference laboratory was taken over by of the Regional BTS Berne. Both schemes send a summary report biannually to the directorate of BTS and the authorities, but the detail information stays within the schemes. The authorities received only a very limited number of reports.

In the Tables 2-6 all the reports from January 1996 to June 2001 to the haemovigilance scheme of BTSSRC and SANZ are summarized. The Tables 12-14 show the incidence of positive viral markers, viral transmission and performed look backs for the last two years. The immunological or bacterial complications caught in the haemovigilance scheme are by no means complete. In contrast, the reports on viral transmission are almost 100% complete. The willingness for participation in the haemovigilance scheme was not very spontaneous, but the reports increased from year to year. Every person active in transfusion medicine easily understands why for example transfusion errors, where human errors often play an important role, are underreported.

The number of the analysed cases is small and therefore conclusions have to be made with caution. They must be interpreted as spontaneous reports with all their advantages and limitations. The reporting frequency was good for serious cases, but lower for non-serious cases (app. 50% serious cases) and the reports of serious cases were more detailed. Well known and in the literature described adverse reactions were reported most frequently. On the other hand, in summer 1996, a case of an unknown type of hypotension was reported. There had been no similar reports in the literature before. This hypotensive reaction of unknown etiology (known reason excluded) gained soon a high attention in literature, especially because it seemed to be connected with filters (special type of filters). In 1999 we received 3 similar reports and subsequently we came in contact with a Canadian group which followed another hypothesis of the etiology of these reactions: they hypothezised that possible individual enzyme defects could be responsible. We had the opportunity to study these cases which have been reported to our haemovigilance system in a spontaneous manner. Results of enzyme analysis (in two cases) didn't show the same defect.

Situation in summer 2001-transitory period

In Summer 2001, in anticipation of the new law it became clear that the authorities want to take over the complete control over all vigilance activities, not only for pharmacovigilance, but also for haemovigilance. Due to the new responsabilities implemented by this new law the pharmaceutical industry quit their financial support to the foundation of SANZ. After the Association of Swiss Medical Association and the Swiss Society of Chemical Industry, the two founder of the SANZ, also decided to stop the financial support of the SANZ, the foundation decided to close the activities of SANZ on 30th June 2001. This meant at the same time the end of our haemovigilance scheme.

In June 2001 the authorities presented a new concept with an own haemovigilance unit associated to the Swiss Federal Office of Public Health (SFOPH) with a new reporting form and procedure. The form demands a lot more details from the clinicians, but also interpretation. It has to be signed by the responsible of the clinic together with the responsible of the blood centre. Late reports sent to SANZ were forwarded to SFOPH. During this period the authorities discussed the new concept with the blood transfusion service. The main problem was how to improve the participation of the hospitals and how to improve the recognition of the clinicians to adverse events. The blood transfusion service has no power to make them comply and for the authorities it isn't easy to make clinicians to comply with the reporting procedure. The blood transfusion service didn't want to hamper the new system of the authorities by an own - parallel - haemovigilance system and want to cooperate as best as possible.

Swiss Health Institute -Swissmedic in the new law of 1.1.2002

With the new law also the structure of the organisation was completely renewed. Swissmedic is the new Drug Regulatory Authority in Switzerland. The new law had taken over all regulations of the 1996 decree. The decisions of Swissmedic are compulsory for the whole country. Swissmedic guarantees quality, safety and efficiency of drugs in Switzerland. It is a centre of competence for drugs, realising an important contribution to a high quality of the health system. According to the law synthetic human drugs, drugs from complementary medicine, biotechnology drugs, drugs for animals, vaccines, blood and blood products, medical devices, implantates (such as pacemaker and endoprothesis), diagnostic reagents, materials (as bandages) are "drugs". This law does not regulate transplants, cells, tissues and xenotranplants. There is one director with four departments. The blood products are controlled by the department of drugs, medical devices and in part by inspectorate and clinical trials.

According to Article 35 (Vigilance) it is mandatory for manufacturers or owner of licence to report:

- Serious adverse events of drugs
- unknown adverse events
- transfusion errors and near miss
- deficiency of quality
- deficiency of materials

How to report:

- the physician in charge of the patien's care informs the hospital laboratory (which has performed the compatibility testing) and the haemovigilance responsible person for the hospital
- information of the blood transfusion service who has produced the blood product
- involvement of other products has to be determined and products have to be recalled

- the official form of Swissmedic has to be signed by user and producer and then send to Swissmedic
- Swissmedic analyses the adverse event and gives a feedback to the hospital

Article 36 determines the reporting terms :

Immediately (within 15 days)

- adverse events resulting in death or life-threatening consequences
- Increased frequency of know adverse events including misuse and intoxication
- Deficiency in quality and all other serious adverse events

Within 60 days in the case of unknown not serious adverse events

In Tables 7-11 the data from Swissmedic are summarized. For 2002 the involved blood products are not yet evaluated. The results of the imputability and the classification has to be interpreted with caution. The assessment was not done by the same person and for the 2002 cases the assessment is not final and some investigations of unclear cases are ongoing.

Discussion

One of the most important prerequisites and the basis of any haemovigilance system is the traceability of all products from donor to recipient and vice versa. This fact is quite good maintained in our country compared to others. But still there isn't a 100% tracability. The delivery to the hospitals is precisely documented, but not in every case it is known if the blood is transfused or destroyed.

One of the important problems is the standardization of the reports for further investigations or comparison. Even standardized forms do not definitively prevent from missing or misinterpreting observations. Forms should be very clear, simple and user-friendly. Collecting information, unnecessary for the analysis and evaluation of an adverse event should be avoided. The information should allow an independent interpretation from a more experienced person in transfusion medicine. The analysis process should be standardized, not only in respect to severity, seriousness and imputability of the adverse events, but also in the interpretation and classification of transfusion reactions. One of the problems are the many existing different grading systems for seriousness. In Switzerland, we are using a system like France with 4 categories (1= absence of immediate or delayed lifethreatening, 2= long term morbidity, 3=lifethreatening 4= death). Another very important concern is the assessment of causality. Not as in France we use only 4 levels: certain (4), probable (3), possible (2), excluded (0), France has a 5 category system: with the 5th category : unlikely (1). But often the information on the reports are just insufficient for a causality assessment and even seriousness is not clear in every case. Transparency and independent analysis is extremely important at any level and especially in cases where human errors are involved. A very important aim is to avoid litigation, but to look for the weakest steps in the transfusion chain and avoid them in future procedures.

In the treatment of many diseases blood transfusion is doubtless lifesaving and indispensable, but in contrast to drugs, the demonstration of effectiveness, best utilization and application is lacking. It would also be interesting to know the best dose for effective transfusion, in view to limited resources and costs. Risks can also be reduced by optimizing the consumption of blood products.

On a local basis, in every small hospital or transfusion unit it is very important to educate the staff involved in blood transfusion to be alert and recognize undesirable or adverse effects. All events should be documented as completely as possible and suspected causes have to be investigated on local basis. Specific procedures should

be defined. Events should be reported independently irrespective of a causative or only suggestive relation to the transfusion. Immediate measures have to be taken. Then the adverse reaction has to be notified to a regional or directly to the national system.

Why do we encounter so often underreporting ? Despite widespread information by the official journal of Swissmedic and several educational meetings together with the blood transfusion service the information on haemovigilance and the law is obviously still insufficient, especially by the users. Sometimes users assume that all adverse events are known. For example, in a chemotherapy or a transplantation unit they know about transfusion reactions and don't report them, because they are frequent and well known. Some hospitals prefer their own local reporting systems and don't see an advantage in a national surveillance of all adverse events. In situations where there are human errors there is still to high fear of consequences. Existing information give the correct assumption that blood products are nowadays safe in terms of viral transmission. But there are still many other risks and we will never achieve a zero risk transfusion situation.

Conclusion

The two periods in our small country show that different regulatory status (mandatory versus spontaneous) and different organizations, are on hand both capable to gather important and helpful information, but on the other hand both schemes are incomplete and face almost the same problems. With the new law the total number of reports is higher. But unfortunately the proportion of the non-serious cases has much more increased than the serious and it has to be assumed that some of the important serious adverse events are still not notified. These observations show how important repetitive information and teaching of haemovigilance is for any reporting scheme. In collecting more complete data, this information could not only give numbers and proportions of risk, they could also lead to the direct prevention and improvement in indication and prevention in the blood transfusion field. Haemovigilance is not an instrument to find mistakes for litigation, but to establish a continuing learning and quality improvement to treat the patient in the best manner.

In order to improve the safety of blood transfusion, haemovigilance systems with particular emphasis on adverse effects of blood transfusion and the misuse of blood products, have been established in several countries in the last couple of years. In blood transfusion, there is a need for a structural surveillance of adverse reactions and for a continuous safety monitoring of transfusion, especially when the seriousness and nature of adverse effects related to blood and blood products like i.e. the transmission of blood-borne diseases is considered. Although, many of the adverse effects are well known today, we do not have exact numbers on the incidence of adverse events and we can only prove by epidemiological data on viral transmissions that blood is safer today than 10 years ago, but not for other undesirable effects like immunological or allergic reactions. Depending on these different backgrounds and aims, there exists no unique definition for the word haemovigilance and almost each country has a different understanding what to include in haemovigilance. For one country surveillance starts with the collection of blood and includes all adverse reactions starting with the donor, other countries include only the immediate act of administration and others look also at all late effects which may be in relation to the administrated blood or blood product. Therefore, important discrepancies concerning the results and experiences are reported from the different established haemovigilance systems and the comparison between different countries is hampered.

Haemovigilance is an important tool in the safety of transfusion medicine and has the potential for considerable improvement of the quality of blood and blood product utilization. But Haemovigilance is a very complex issue with many different aspects to

consider and many different players. The aim is to make all information concerning blood and transfusion issues and conclusions driven by haemovigilance systems available to all European countries. To achieve this aim an approach to coordinate and harmonize has to be made as soon as possible. The different haemovigilance network should not stop at the border of each country. The European Haemovigilance Network Group has set up already a good start.

Table 1
Blood donation and use of blood products

	1998	1999	2000	2001
Whole Blood Donations	435,968	437,966	434,209	415,345
Autologous Donations	15,540	13,425	12,069	10,395
Apheresis	12,069	15,550	18,650	16,764
Red Cells	305,227	294,941	283,083	311,448
FFP	76,617	77,257	80,176	97,043
Platelets	59,804	57,778	74,770	91,641
Plasma Fractionation (1)	52,026	43,176	74,770	85,578

Table 2

Reported by	1996	1997	1998	1999	2000	2001*	TOTAL
Hospital	9	9	14	20	16	12	**80**
Blood Transfusion Service	2	5	4	5	3	0	**19**
Family Doctor	0	0	0	1	0	0	**1**

Table 3

Involved Blood Product	1996	1997	1998	1999	2000	2001*	TOTAL
Red Blood Cells buffy coat-free	4	10	15	6	0	0	**35**
Red Blood Cells leucodepleted	0	0	0	10	8	6	**24**
Fresh Frozen Plasma	1	3	2	5	5	1	**17**
Platelet by Apheresis	0	1	1	2	6	5	**15**
Platelet by Buffycoat preparation	6	0	0	3	0	0	**9**
TOTAL	**11**	**14**	**18**	**26**	**19**	**12**	**100**

Table 4

Seriousness	1996	1997	1998	1999	2000	2001*	TOTAL
Serious (life threatening, death)	8	5	2	8	5	4	**32**
Non Serious	3	9	16	18	14	8	**68**

Table 5

Imputability	1996	1997	1998	1999	2000	2001*	TOTAL
Proven	0	2	3	5	3	1	**14**
Probable	5	5	3	9	9	2	**33**
Possible	5	5	10	6	4	6	**36**
Unprobable	1	2	2	6	3	3	**17**

Table 6

Adverse Event	1996	1997	1998	1999	2000	2001*	TOTAL
Transfusion Error / Hemolysis	0	2	3	4	3	1	**13**
Hypotension / Shock	6	0	0	3	0	1	**10**
Bacterial Contamination	0	2	0	1	0	1	**4**
Allergic Reaction	1	2	3	5	6	5	**22**
Pulmonary Oedema / TRALI	0	2	0	2	1	3	**8**
Febrile Non-Hemolytic Reaction	1	4	9	4	5	0	**23**
Volume Overload	0	0	1	2	0	0	**3**
Viral Transmission (HIV, HBV)	2	0	0	0	1	0	**3**
Antibody (HPA-1a)	0	0	0	1	0	0	**1**
Without Causality	1	2	2	4	3	1	**13**
TOTAL	**11**	**14**	**18**	**26**	**19**	**12**	**100**

Table 7

Reported by	2001
Hospital	58
Blood Transfusion Service	5

2002 not yet evaluated

Table 8

Involved Blood Products	**2001**
Red Blood Cells leucodepleted (RBC)	34
Platelet Concentrate (PC)	7
Fresh Frozen Plasma (FFP)	4
RBC + FFP	1
PC + RBC + FFP	1
RBC + PC	1
Transplants	3
Stem Cells	2
Unknown	11

2002 not yet evaluated

Table 9

Imputability	**2001** (1.7.2001 - 31.12.2001)	**2002** (1.1.2002 - 1.11.2002)
Proven	19?	0?
Probable	29	16
Possible	12	70
Unprobable	3	20

Table 10

Seriousness	**2001** (1.7.2001 - 31.12.2001)	**2002** (1.1.2002 - 1.11.2002)
Serious (life threatening, death)	12	5
Non Serious	51	101

Table 11

Adverse Event	**2001** (1.7.2001 - 31.12.2001)	**2002** (1.1.2002 - 1.11.2002)
Transfusion Error	13	5
Hemolytic Reaction	7	2
Anaphylaxis	0	3
Bacterial Contamination	9	4
Allergic Reaction / Urticaria	16 *	33
Pulmonary Oedema / TRALI	0	3
Febrile Non-Hemolytic Reaction	9	33
Volume Overload	0	3
Graft-Versus-Host-Disease	3	0
Without Causality / Not Classified	6	20
TOTAL	**63**	**106**

* possibly also anaphylaxis

Table 12

Marker	**1999**		**2000**		**2001**	
Anti-HIV total	5		4		7	
New donor	4		3		1	
Of 1000 donations	0.11	0.130	0.009	0.100	0.030	0.016
HBsAg total	45		41		41	
New donor	34		32		34	
Of 1000 donations/regular	0.10	0.017	0.090	0.021	0.017	0.090
Anti-HCV	52		41		23	
New donor	33		33		22	
Of 1000 donations/regular	0.11	0.045	0.090	0.019	0.050	0.002
ALAT	4104		4884			
Of 1000 donations/regular	12.8		12.4			

Table 13
Look back procedures (donor related)

Marker	number of notified LB 2000	transfusion ass. infections 2000	remarks	number of notified LB 2001	transfusion ass. infections 2001	remarks
HIV	2	0		4	1	1 not com
HCV	5	0	3 not com *	3		3 not com
HBV	6	0	1 not com	2	0	1 not com
Malaria	1	0				
CJD				4	n.a.	2 not com

* not completed

Table 14
Look back procedures (patient related)

Marker	2000	poss	prob	excl	not ex	remark	2001	poss	prob	excl	not ex	remark
HIV	3			3			5			2	2	1 n.c.
HCV	39	1		18	5	14 n.c.*	21	1		10	4	6 n.c.
HBV	10		1	4	2	3 n.c.	6			4		2 n.c.
HIV/HCV	1	1										

* not completed

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