Journal of Clinical Toxicology
ISSN: 2161-0495

Aagaard et al., J Clinic Toxicol 2012, 2:2
DOI: 10.4172/2161-0495.1000120

Research Article Open Access

Pharmaceutical Production Problems Detected by Adverse Drug Reactions Reports: A Documentary Study from the German Democratic Republic, 1982 to 1990

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Abstract

Objectives: To characterise spontaneous adverse drug reactions (ADRs) reported in the former German Democratic Republic (GDR) and to identify ADRs related to quality problems with pharmaceuticals.

Material and methods: In 1964 a spontaneous ADR reporting system was established in the GDR with the purpose to collect information about possible toxic and damaging ADRs from medicine use. The spontaneous reporting system was also seen as an important tool for securing the quality of the pharmaceutical production. Data on ADRs occurring in the GDR were located in the national German archive, Bundesarchive in Berlin. Only ADR reports submitted from 1982 to 1990 were identified. The reports were analysed with respect to type of ADR (System Organ Class [SOC]) and substance.

Results: From 1982 to 1990 a total of 3990 ADR reports covering information about 6706 ADRs were submitted to the GDR health authorities. The largest share, 26% of all ADRs referred to the SOC "*skin and subcutaneous disorders*", followed by the SOCs "*general disorders and administration site conditions*" (23% of total ADRs) and "*gastrointestinal disorders*" (11% of total ADRs). Two-thirds of all ADRs were related to the therapeutic groups: "*anti-infectives for socs use"* (ATC group J) and "*blood and blood forming organs"* (ATC group B). Approximately 85% of ADRs from ATC group B was reported for dextran 40, the majority of these ADRs of the general type, followed by skin ADRs and ADRs concerning respiratory disorders. Additionally a high number of circulatory collapse/shock were reported for dextran 40. The increased level of ADR reporting was related to an abnormal distribution of low and high molecules of dextran 40 occurring due to production problems. Fifteen percent of ADRs were reported for radiographic contrast media; the majority for the substance amidotrizoate, and more than one half of these were of the type skin and respiratory disorders.

Conclusion: In the GDR during the 1980s, the spontaneous ADR reporting system managed to detect serious pharmaceutical quality problems in dextran products. The products of lower quality could not be replaced easily due to lack of safer national alternatives as well as lack of foreign currency necessary to import of purer products from Western countries.

Keywords: Pharmacovigilance; Spontaneous Reporting Systems; German Democratic Republic; Pharmaceutical Quality; Dextran; Contrast Media

Introduction

The German Democratic Republic (GDR) (1949 to 1990) was known for its well developed pharmaceutical industry organized in state-owned companies that produced several pharmaceuticals, both original as well as generic products [1]. The generics were copies of pharmaceuticals already marketed 3 to 5 years previously in western countries and had to follow the international patent law [2]. Efficacy and safety assessments of generics were based on existing international data [1-2]. From 1951 to 1989 a total of 48 original products were developed by the GDR pharmaceutical industry, e.g. the anabolic steroid *chlordehydromethyltestosteron* (Oral-Turinabol®) and the beta-blocker *talinolol (*Cordanum®) [1]. Despite the difficult financial situation after World War II innovative product development increased in the 1960s and 1970s resulting in an expansion of the GDR pharmaceutical industry [3]. However over the time, the temporary lack of chemicals, packing material, limited capacities for pharmacological and toxicological testing and production equipment restricted the further expansion [4]. Good Manufacturing Practice (GMP) and Good Laboraty Practice (GLP) based on the World Health Organization (WHO) standards were implemented in the GDR [5]. In the 1960s systems for the reporting of adverse drug reactions (ADRs) were established at national level, and internationally by the WHO, to collect information about ADRs following medicine use, particularly with regard to rare and serious reactions [6]. To comply

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Received February 16, 2012; **Accepted** February 24, 2012; **Published** February 28, 2012

Citation: Aagaard L, Meyer U, Schaefer M, Hansen EH (2012) Pharmaceutical Production Problems Detected by Adverse Drug Reactions Reports: A Documentary Study from the German Democratic Republic, 1982 to 1990. J Clinic Toxicol 2:120. doi:10.4172/2161-0495.1000120

with the WHO recommendations in the GDR a similar ADR reporting system was introduced in 1964 like in other countries, with the purpose to collect information about possible toxic and harmful ADRs from medicine use [5]. In addition in the GDR the spontaneous reporting system was also viewed as an important tool for securing the quality of the pharmaceutical production [7]. Internationally, only limited information about ADRs reported in the GDR as well as and other Eastern European countries has been available [8]. The fall of the Berlin wall has allowed access to reports on ADRs, that previous was treated as state secrets and with access to only a few people. The objective of this study was to characterise spontaneous ADRs reported in the GDR with respect to type of reported ADRs and suspected substances, and to identify ADRs related to quality problems with pharmaceuticals.

Setting

The pharmaceutical industry and medical supply system in the GDR

The GDR pharmaceutical industry was organized through a cooperation of all major pharmaceutical companies named GERMED with its main center at the Arzneimittelwerk (AWD) Dresden [3]. GERMED constituted 12 pharmaceutical factories and within GERMED specialization concerning therapeutic areas was supported. Berlin Chemie maintained the insuline production and Jenapharm the production of hormones and antibiotics [3]. Another form of specialization referred to the way of administration or dosage form of the medication, i.e. the production of eye drops and inhalation sprays were maintained by Ankerwerk Rudolstadt, suppositories and ovules by Pharmamed Naumburg and liquids by the company Ysat Wernigerode [3]. In the GDR prescription medicines were dispensed to patients free of charge and over-the- counter medicines were sold at low prices through state-owned pharmacies [9]. Approximately 75 % of licensed medications were prescription only [9]. In 1949 approximately 5000 medications was produced in the GDR, but this number was reduced much heavily to around 1700 in 1951, as only medications which were considered rational with respect to efficacy and safety were allowed to remain on the market [9]. The licensed medications were listed in the national medication compendium, the "Arznemittelverzeichnis", which was issued annually [9]. Table 1 displays the distribution of the number of licensed pharmaceutical products in the GDR distributed by different manufacturers and listed in the "Arzneimittelverzeichnis" [9]. For a small country like the GDR, which did not have the economic power to have a pharmaceutical industry large enough to cover the need for all needed medical supplies within the GDR a considerable number of pharmaceuticals was also imported from other Eastern European countries as well as non-socialist countries [4]. Over the years, approximately 1750 medications (range 1440 to 2043) were licensed for use in the GDR. Of these medications around 1000 (range 1343 to 1900) were produced by the GDR pharmaceutical industry and some of these even produced by local pharmacies called "Standardrezepturen" [4]. Another 250 pharmaceutical products (range 108 to 244) were imported from other socialist countries and about 200 (range 17 to 399) from non-socialist countries [4].

GDR national ADR reporting system

In 1964 a national ADR surveillance program was established by law by the GDR's Ministry of Health and in 1969 an official ADR reporting form was launched together with information about the importance of reporting ADRs [7, 9-11]. Initially physicians and pharmacists were requested to report ADRs however reporting was voluntary. In 1981, in order to increase the number of submitted ADR reports, mandatory reporting was introduced for physicians [8]. To submit an ADR report the following information was required: age and gender of the patient; severity and characteristics of the ADR(s), suspected medicine and also concomitant medicines, indication for use, dosage, treatment period, date of onset of the ADR, causality assessment and other

Year	GDR productions	Pharmaceuticals imported from Eastern Europe	Pharmaceuticals imported from Western countries	Total
1951	1900	NR	NR	1900
1954	1511	NR	NR	1511
1957	1685	NR	NR	1685
1959	1680	NR	NR	1680
1961	1440	NR	NR	1440
1962	NA	NA	NA	NA
1969	NA	NA	NA	NA
1970	NA	NA	NA	NA
1971	1397	108	17	1522
1972	1397	108	17	1522
1973	NA	NA	NA	NA
1974	NA	NA	NA	NA
1975	NA	NA	NA	NA
1976	1348	148	29	1525
1977	NA	NA	NA	NA
1979	NA	NA	NA	NA
1980	1343	141	26	1510
1981	1367	204	249	1820
1982	NA	NA	NA	NA
1983	NA	NA	NA	NA
1984	NA	NA	NA	NA
1988	1392	244	234	1870
1990	1412	232	399	2043

NR: not reported; NA: data not available

Table 1: Licensed pharmaceutical products (number) in the German Democratic Republic distributed by type of producer, listed in the national medicines compendium.

relevant information such as laboratory data if available [8]. All reports were made on paper as at that time no electronic reporting system or reporting by the telephone was established. The spontaneous reporting system was managed by the "Institut für Arzneimittelwesen der DDR" (IFAR) [8]. All suspected cases, including unknown ADRs, serious ADRs, ADRs due to interactions with other drugs, and ADRs resulting in endangering of life or resulting in death were to be reported and centrally documented [11]. Formal assessments of ADR reports were initiated in 1977. Scientific staff working at IFAR evaluated the reports and if the reported ADRs were suspected to be caused by defects in quality of the medicines, further investigations were initiated. All other cases were examined by the "Problem commission of Clinical Pharmacology" located in Dresden [11]. Hence the majority of ADR reports were only tracked in special cases, and no general practice for analysing these cases existed. Results of the internal analysis were usually not published and written feed-back was only provided to the reporter and pharmaceutical companies in cases where the ADRs were caused by a quality defect of the administered drug [11]. This system was in place until the German Reunification in October 1990. The GDR joined the international WHO collaboration on drug safety in 1983 and from the summer of 1985 until 1990 selected ADR cases were forwarded to the WHO database. The intention of the selection process was that only new ADRs should be reported to avoid "unnecessary"overreporting. The characteristics of these ADR cases have been reported elsewhere [8]. Table 2 lists selected cases of serious ADR cases leading to withdrawal of the products from the market in the GDR. Decisions of withdrawal were made on the basis of both own and international observations on serious ADRs.

Material and Methods

Data on ADRs reported in the GDR were provided from several sources and types of material. Material was searched in the national German archives, *Bundesarchive,* in Berlin as well as databases and websites. All relevant identified material was retrieved. The analysed material covered the period from 1964 to 1990 and derived from two main sources: a) ADR data reported in the German Democratic Republic from 1982 to 1990 and b) reports and correspondences between GDR health authorities and pharmaceutical companies and other relevant stakeholders. Information about ADRs occurring in the GDR and reported to IFAR from 1982 to 1990 was retrieved. Documents from 1969 to 1981 could not be located in the archive although former employees of the IFAR had confirmed that all files were stored in the Bundesarchive after the reunification (personal communication). Furthermore, we were not able to get copies of the original ADR reports, but were allowed access to extracts of information which had been manually entered into protocols by IFAR employees at the time of reporting. In these protocols information about suspected medications, batch number, reported ADRs, deaths and whether the reports had been forwarded to the Prague Pharmacovigilance centre and/or the WHO ADR database VigiBase was present. For some of the ADR reports information about evaluation patterns as well as established quality problems for the reported batches was found, however, this information was not systematically documented, and therefore could not be included in this study.

Analysis

Data were extracted from the ADR register and protocols into Excel files using the following categories: ATC (anatomical therapeutic chemical) [12] code of medications, trademark and active substance of the medicines, ADRs coded according to MedDRA terminology at System Organ Class (SOC) level [13]. The process was very time consuming due to the large amount of data which were written in German language and had to be translated into English. In order to present the large amount of data in a comprehensive way, the medicines for which the ADRs are reported are presented at ATC level 1. Information about seriousness of reported ADRs as well as age and sex of patients was not available in the ADR protocols of IFAR.

Results

From 1982 to 1990 a total of 3990 ADR reports (range 233 to 537 per year) covering information about 6706 ADRs (range 373 to 926) were submitted to the GDR health authorities. Approximately 60% of ADR reports concerned inpatients and 40 % outpatients. On average, 10 fatal ADR cases were reported per year (range 7 to 20). Table 3 displays the number of ADRs reported in the GDR from 1982 to 1990 classified according to the affected system organ class (SOC) and the therapeutic groups. The largest share, 26% of all ADRs referred to "*skin and subcutaneous disorders*", followed by the SOC "*general disorders and administration site conditions*" (23% of total ADRs) and "*gastrointestinal disorders*" (11% of total ADRs).

Year of marketing	Year of withdrawal	Medication (s)	Substance (s)	Adverse drug reaction (s)	GDR cases (N)
1966	1984	Enteroseptol Entero-Vioform Mexaform plus	Clioquinol Dichlorquinol	SMON* syndrome	0
1969	1984	Aminophenazone Oramon Pulmophyllin	Aminophenazone	Carcinogenic	0
< 1960	1984	Perclusone Wofapyrin	Phenylbutazone combinations	Bone marrow supression	11
1969	1984	Ketazon	Kebuzon	Bone marrow suppression	0
1981	1985	Sotropin H	Somatrotopin	Creutzfeld-Jacob Syndrome	0
1984	1985	Auroplex	Lindane	CNS reaction	5
1979	1985	Phenoro	Canthaxanthin	Retina sediments	3
< 1960	1986	Benedorm	Pyrithyldion	Dependence	1
< 1960	1986	Bromisoval (Alluval)	Bromisovalerianyl	Dependence	0
< 1960	1988	Phenylbutazone	Phenylbutazone	Bonemarrow suppression	84 (3 fatal)

*Sub-acute myelo-optico neuropathy

Table 2: Medications marketed in the German Democratic Republic (GDR) but withdrawn due to negative risk-benefit evaluations by health authorities, selected cases 1982 to 1990.

ATC/System Organ Class	Blood	Card.	Cong.	Ear	Eye	Gen.	Gastr.	Hepa	Imm.	Inf.	Inj.	Inv.	Met.	Mus.	Nerv.	Preg.	Psyc.	Renal	Resp.	Repr.	Skin	Social	Surg.	Vasc.	Total
Alimentary tract & metabolism (A)																									
A01/A02/A03/A04	0	9	0	0	3	11	11	1	1	0	0	2	0	2	16	1	4	0	2	1	11	0	0	0	75
A06/A07/A08/A09	4	3	0	0	0	5	14	4	1	1	0	0	0	0	5	0	0	0	15	0	15	0	0	3	70
A10/A11	1	3	0	0	0	26	5	0	7	1	1	3	3	0	6	0	1	1	0	3	34	0	0	3	98
A12/A14/A16	1	2	0	0	0	2	8	1	0	1	0	0	0	1	2	0	0	0	2	0	3	0	0	2	25
Total A	6	17	0	0	3	44	38	6	9	3	1	5	3	3	29	1	5	1	19	4	63	0	0	8	268
Blood & blood forming organs (B)																									
B01	8	3	0	0	0	44	12	3	3	1	0	6	0	4	7	0	0	0	4	1	25	0	6	9	136
B02	1	4	0	0	0	8	2	0	5	0	0	1	0	0	0	0	0	0	9	0	1	0	0	4	35
B03	1	3	0	0	0	54	28	0	3	4	0	5	0	0	5	0	2	2	9	0	6	0	0	9	131
B05/06	1	108	0	1	9	554	122	0	104	11	2	96	0	14	41	4	9	7	187	0	227	0	2	103	1602
Total B	18	118	0	1	9	660	164	3	115	16	2	108	0	18	53	4	11	9	209	1	259	0	8	125	1904
Cardiovascular system (C)																									
(C01	1	8	0	0	2	10	15	0	3	0	1	1	0	0	8	0	0	0	5	2	15	0	0	5	76
C02	4	1	0	0	3	8	13	42	3	1	0	1	0	0	8	0	2	3	3	0	11	0	0	0	103
C03/C04/C05	1	8	0	0	2	8	31	0	9	0	0	5	0	3	13	0	0	1	1	0	36	0	0	2	120
C07/C08/C09/C10	0	4	0	1	4	11	13	4	3	1	0	0	0	3	11	0	3	0	3	2	33	0	0	1	97
Total C	6	21	0	1	11	37	72	46	18	2	1	7	0	6	40	0	5	4	12	4	95	0	0	8	396
Dermatologicals (D)																									
D01/D02/D03	1	0	0	0	2	2	5	0	0	1	0	0	0	1	3	0	1	0	0	0	16	0	0	0	32
D04/D05	0	1	0	0	3	3	20	0	0	0	0	1	0	0	3	0	0	0	0	0	7	0	0	0	38
D06/D07	0	0	0	0	0	5	1	0	0	1	0	0	0	3	1	0	0	0	1	0	7	0	0	1	20
D08/D11	0	0	0	0	0	2	0	0	2	0	0	0	0	0	1	0	0	0	0	0	61	0	0	0	66
Total D	1	1	0	0	5	12	26	0	2	2	0	1	0	4	8	0	1	0	1	0	91	0	0	1	156
Sex hormons (G)																									
G01/G02	0	0	0	0	0	3	2	0	0	0	0	0	0	0	2	0	1	0	1	0	4	0	0	4	17
G03/G04	0	2	0	0	1	29	10	10	1	0	0	1	0	2	4	0	0	0	0	0	20	0	0	7	87
Total G	0	2	0	0	1	32	12	10	1	0	0	1	0	2	6	0	1	0	1	0	24	0	0	11	104
Systemic hormonal prep. (H)																									
H01/H02	0	9	0	0	0	31	9	0	2	1	0	4	0	1	5	0	1	0	16	0	29	0	0	9	117
H03/H04	1	2	0	0	0	3	2	2	0	0	0	0	0	0	1	0	0	0	0	0	9	0	0	1	21
Total H	1	11	0	0	0	34	11	2	2	1	0	4	0	1	6	0	1	0	16	0	38	0	0	10	138
Anti-infectives for systemic use (J)																									
J01	11	24	1	3	11	158	77	25	53	12	0	10	0	7	38	0	4	1	40	1	334	0	1	26	837
J02/J04/J05/J06	4	1	0	0	0	53	3	1	3	6	0	0	0	5	5	0	0	3	1	0	31	0	0	4	120
J07	15	25	1	3	11	211	80	26	56	18	0	10	0	12	43	0	4	4	41	1	365	0	1	30	957
Total J	30	50	2	6	22	422	160	52	112	36	0	20	0	24	86	0	8	8	82	2	730	0	2	60	1914
Antineoplastic & immuno. (L)																									
L01/L02/L04	3	4	0	0	0	18	4	3	4	4	0	1	0	0	4	0	0	0	5	0	17	0	0	2	69
Total L	3	4	0	0	0	18	4	3	4	4	0	1	0	0	4	0	0	0	5	0	17	0	0	2	69
Musculoskeletal system (M)																									
M01	12	10	0	0	0	40	56	25	4	12	0	5	0	4	15	0	4	2	10	0	64	0	0	16	279
M02/M03/M04	2	8	0	0	1	19	42	0	5	0	6	1	0	3	11	0	3	0	2	0	37	0	0	1	161
Total M	14	18	0	0	1	59	118	25	9	12	6	6	0	7	26	0	7	2	12	0	101	0	0	17	440
Nervous system (N)																									
N01	2	10	0	0	1	45	12	5	13	2	0	10	0	0	35	0	3	0	14	0	37	1	0	19	209
N02	9	16	1	2	1	48	17	4	18	1	1	4	0	2	18	0	3	2	14	0	72	0	0	15	248
N03	2	2	0	1	3	17	20	6	3	0	0	1	0	0	16	0	5	1	1	0	31	0	0	0	109
N04/N05/N06/N07	17	11	0	0	3	34	23	7	2	1	1	4	0	0	25	0	13	1	5	0	13	0	1	12	173
Total	30	39	1	3	8	144	72	22	36	4	2	19	0	2	94	0	24	4	34	0	153	1	1	46	739

Antiparastic (P)																									
P01	5	2	0	0	0	3	3	0	0	0	0	0	0	0	2	0	2	1	2	0	3	0	0	1	24
P02	1	0	0	0	0	1	8	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	14
P03	1	0	0	0	4	1	3	0	0	0	0	0	0	2	5	0	2	0	1	0	4	0	0	2	25
Total P	7	2	0	0	4	5	14	0	0	0	0	0	0	3	8	0	4	1	3	0	8	0	0	4	63
Respiratory system																									
R01/R02/R03	0	10	0	0	0	34	16	0	2	1	0	4	0	3	9	0	7	0	87	0	38	0	0	19	230
R05/R06	0	4	0	0	11	4	8	0	0	0	0	0	0	0	3	0	5	0	3	0	12	0	0	0	50
Total	0	14	0	0	11	38	24	0	2	1	0	4	0	3	12	0	12	0	90	0	50	0	0	19	280
Sensory organs (S)																									
S01	0	1	0	0	28	2	0	0	1	0	0	1	0	0	0	0	0	0	1	0	17	0	1	2	54
Total S	0	1	0	0	28	2	0	0	1	0	0	1	0	0	0	0	0	0	1	0	17	0	1	2	54
Various (V)																									
V01/V03/V04	0	10	0	0	3	100	33	1	8	0	1	15	0	0	11	0	0	2	19	0	37	0	0	23	263
V06	0	7	0	0	0	55	5	0	1	5	0	5	0	0	3	0	0	1	11	0	13	0	0	2	108
V08/V09/V10	6	27	0	0	9	77	132	3	43	1	2	29	0	3	39	0	8	2	71	0	165	0	0	61	678
Total V	6	44	0	0	12	232	170	4	52	6	3	49	0	3	53	0	8	5	101	0	215	0	0	86	1049
Others	5	2	0	0	5	18	5	2	12	4	0	2	1	2	2	0	3	1	4	0	109	0	0	4	181
Total	121	300	3	11	108	1525	720	171	323	85	12	179	4	75	374	5	82	30	489	11	1755	1	12	317	6706

Abbreviations and definitions used in table 3

System organ class

Blood: Blood and lymphatic system disorders; Card: Cardiac disorders; Cong: Congenital, familial and genetic disorders; Ear: Ear and labyrinth disorders; Eye: Eye disorders; Gen: General disorders and administration site conditions; Gastr: Gastrointestinal disorders; Hepa: Hepatobiliary disorders; Imm: Immune system disorders; Inf: Infections and infestations; Inj:Injury, poisoning and procedural complications; Inv: Investigations; Met: Metabolism and nutrition disorders; Mus:Musculoskeletal and connective tissue disorders; Nerv: Nervous system disorders; Preg:Pregnancy, puerperium and perinatal conditions; Psyc:Psychiatric disorders; Renal: Renal and urinary disorders; Resp:Respiratory, thoracic and mediastinal disorders; Repr:Reproductive system and breast disorder; Skin:Skin and subcutaneous tissue disorders; Social:Social circumstances; Surg:Surgical and medical procedures; Vasc:Vascular disorders.

Anatomical therapeutic chemical code

A01: Stomatological preparations; A02: Medicines used for acid related disorders; A03: Medicines used for functional gastrointestinal disorders; A04: Antimetics and antinausants; A06: Laxatives; A07: Antidiarrheals; A08: Antiobesity preparations; A09: Digestives; A10: Medicines used in Diabetes; A11: Vitamins; A12: Mineral supplements; A14: Anabolic agents for systemic use; A16: Other alimentary tract and metabolism products.

B01: Antithrombotic agents; B02: Antihemorrhagics; B03: Antianemic preparations; B05: Blood substitutes and perfusion solutions; B06: Other haematological agents; C01: Cardiac therapy; C02: Antihypertensives; C03: Diuretics; C04: Peripheral vasodilators; C05: Vasoprotectives; C07: Beta blocking agents; C08: Calcium channel blockers; C09: Agents acting on the renin-angiotensin system; C10: Lipid modifying agents.

D01: Antifungals for dermatological use; D02: Emollients and protectives; D03: Preparation for treatment of wounds and ulcers; D04: Antipruritics; D05: Antipsoriatics; D06: Antibiotics and Chemotherapeutics for dermatological use; D07: Corticosteroids; D08: Antiseptics and desinfectants; D11: Other dermatological preparations; G01: Gynaecological anti-infective and antiseptics; G02: Other gynaecological; G03: Sex hormones and modulators of the genital system; G04: Urologicals; H01: Pituitary and hypothalamic hormones and analogues; H02: Corticosteroids for systemic use; H03: Thyroid therapy; H04: Pancreatic hormones; J01: Antibacterials for systemic use; J02: Antimycotics for systemic use; J04: Antimycobacterials; J05: Antivirals for systemic use; J06: Immune sera and immunoglobulins, J07: Vaccines; L01: Antineoplastic agents; L02: Endocrine therapy; L04: Immunosuppressants; M01: Antiinflammatory and antirheumatic products; M02: Topical products for joint and muscular pain; M03: Muscle relaxants; M04: Antigout preparations; N01: Anaesthetics; N02: Analgesics; N03: Antiepileptics; N04: Anti-Parkinson medications; N05: Psycholeptics; N06: Psychoanaleptics; N07: Other nervous system medications; P01: Antiprotozoals; P02: Anthelmintics; P03: Ectoparasiticides; R01: Nasal preparations; R02: Throat preparations; R03: Medicines used for obstructive airway diseases; R05: Cough and cold preparations, R06: Antihistamines for systemic use; S01: Ophthalmologicals; V01: Allergens; V03: Other therapeutic products; V04: Diagnostic agents; V06: General nutritients, V08: Contrast media; V09: Diagnostic radiopharmaceuticals; V10: Surgical dressings.

Table 3: Adverse drug reactions (N) reported in the German Democratic Republic distributed by therapeutic group (Anatomical Therapeutical Chemical Code [ATC]) and type (system organ class) 1982 to 1990.

ADRs by therapeutic group

Two-thirds of all ADRs were seen in the therapeutic groups: "*anti-infectives for systemic use*" (ATC group J), predominantly antibacterials (ATC group J01) and vaccines (ATC group J07) and "*blood and blood forming organs*" (ATC group B). Approximately 15% of ADRs were reported for medications from ATC group V (various), particularly for contrast media agents (ATC group V08). Within ATC group B the majority of ADRs was reported for plasma volume expanders, particularly dextrans (N = 773). Table 4 displays the characteristics of ADRs reported for dextran containing products marketed in the GDR reported from 1982 to 1990. The majority of reports, 83% of total ADRs was reported for dextran 40, followed by 11% of ADRs reported for dextran 40/mannitol, and 6% of reports were reported for dextran 75. For dextran 40, the majority of reported ADRs were of the type "general disorders and administration site conditions" (N = 181), i.e. chills and temperature changes; followed by ADRs concerning skin reactions (N = 108) and ADRs concerning respiratory disorders (N= 101). A large number of circulatory collapse/shock (N = 39) and anaphylactic reactions (N= 25) was also reported for dextran 40. Table 5 displays the characteristics of ADRs for the contrast media agent amidotrizoate natrium in the GDR from 1982 to 1990. The majority of ADRs (23% of total ADRs) were of the type skin disorders, i.e. urticaria followed by gastrointestinal ADRs (vomiting and nausea) (21% of total) and respiratory ADRs (11% of total), i.e. difficulty breathing.

System Organ Class	Dextran 40	Dextran 40, 100 mannitol	Dextran 75
Cardiac disorder	Bradycardia (6)	Decreased heart Rhythm (1)	Atrial fibrillation (1)
	Cardiac disorder (13)	Tachycardia (6)	Tachycardia (1)
	Palpitation (1)	Heart race (1)	Cardiac disorder (2)
	Tachycardia (28)		
Total	48	8	4
Eye disorders	Conjuctivitis (2)	NR	NR
	Eye burning (2)		
	Pupil dilatation (1)		
Total	5	0	0
General disorders	Chills (88)	Chills (10)	Injection site reaction (1)
	Dead (1)	Temperature increased (6)	Chills (2)
	Dizziness (1)	Pain (1)	Temperature increased (3)
	Temperature changes (79)	Injection site reaction (1)	
	Head pressure (1)	Fever (1)	
	Pain (5)		
	Hypotonie (3)		
	Incompability (1)		
	Lack of consciousness (2)		
Total	181	19	6
Gastrointestinal disorders	Vomiting (42)	Stomach pain (1)	Nausea (2)
	Stomach pain (2)	Nausea (3)	Vomiting (1)
	Nausea (29)	Vomiting (2)	
	Mouth blister (2)		
	Hyperstomie (1)		
	Diarrhea (4)		
Total	80	6	3
Infections and infestations	Flu symptoms (1)	NR	Pyrogen reaction (1)
	Pyrogen reaction (2)		
Total	3	0	1
Investigations	Blood pressure increased (10)	Increased pulse (1)	Decreased blood pressure (1)
	Pulse changes (3)	Blood pressure changes (6)	Hypertension (1)
Total	13	7	2
Immune system disorders	Anaphylactic reaction/shock (25)	Anaphylactic reaction/shock (4)	Anaphylactic reaction/shock (11)
Total	25	4	11
Musculoskeletal disorders	Muscle pain (24)	Back pain (1)	NR
Total	24	1	0
Nervous system disorders	Parasthesies (2)	Headache (3)	Convulsions (1)
	Headache (4)	Restlessness (1)	
	Vertigo (1)	Uterus contraction (1)	
	Restlessness (2)		
	Tingling (2)		
	Trembling (1)		
Total	12	5	1
Psychiatric disorders	Psychiatric disorder (2)	Anxiety (1)	Anxiety (1)
Total	2	1	1
Renal and urinary disorders	Kidney pain (3)	Kidney pain (2)	NR
Total	3	2	0
Respiratory disorders	Bronchospasm (74)	Lung oedema (2)	Difficulty breathing (11)
	Cough (3)	Difficulty breathing (8)	
	Cyanosis (17)	Cyanosis (2)	
	Lung oedema (7)		
Total	101	12	1
Skin and subcutaneous disorders	Urticaria (22)	Skin redness (3)	Erythema (1)
	Rash (2)	Urticaria (1)	Hot flashes (1)
	Pruritus (26)	Exanthem (5)	Lip oedema (1)
	Swelling (3)	Hot flashes (1)	Rash (3)
	Erythem (5)	Oedema (3)	
	Oedema (10)		
	Blister (8)		
	Hot flashes (1)		

	Exanthem (26) Itching (5)		
Total	108	13	6
Vascular disorders	Circulatory collaps/schock (39)	Circulatory collaps/schock (4)	NR
Total	39	4	0
Total ADRs (N)	645	82	46

Table 4: Characteristics of adverse drug reactions (N) reported for dextrans containing products reported from 1982 to 1990 in the German Democratic Republic (numbers in brackets).

Discussion

This is the first study which retrospectively has evaluated spontaneous ADR reports submitted to the national health authorities in the GDR from 1982 to 1990. The GDR spontaneous reporting system was well functioning and able to detect production problems in the pharmaceutical industry. Analysis showed that the majority of ADR reports were found related to dextran 40 products as well as contrast media agents. As only limited information in the archives about age and gender of the patients affected by the reported cases as well as seriousness of reported ADRs was available we focus on the following aspects of ADR reporting:

Number of reported ADRs

The reported ADRs corresponds to an annual reporting rate of 27 reports/million inhabitants/year which is low compared to the number of licensed medicines in the GDR and the size of the population. In the same period the reporting rate in West Germany was 89 reports/million inhabitants/year [11]. Within the Comecon countries reporting rates varied widely, from 7 reports/million inhabitant/year in the Soviet Union to 243 reports/million inhabitants/year in Czechoslovakia [11]. Spontaneous reporting systems are known to be biased by underreporting [14]. In the GDR information about medications, both efficacy and safety topics were published in the medical journal "Medicamentum" which was issued monthly by the GDR pharmaceutical industry. This practice may have contributed to underreporting, because the GDR physicians might have assumed that everything of importance was already known. Despite the low number of ADR reports, the reported ADRs were in line with ADRs reported in other countries with respect to type and suspected medications.

ADRs reported for dextrans

This study showed that spontaneous ADR reports had detected quality problems in relation to the production of dextran 40 at Serumwerk Bernburg. In the 1960s it was known that an abnormal distribution of low and high dextran molecules could lead to an increased risk of serious ADRs such as shock and vascular disturbances when infused in children and pregnant women [15-18], and guidelines for handling serious ADRs were published [19]. In the 1970s the number of reports on ADRs such as anaphylactic shocks, bronchospasm, and circulatory collapses/shocks reported for dextran 40 increased in the GDR. Internationally only few studies analysing spontaneous ADRs from use of dextrans has been reported [19-21]. In the US 366 reports, 25% of these being serious, was reported for dextran 40 and dextran 70 from 1969 to 2004 [20]. The majority of serious ADRs were anaphylaxis/anaphylactic events [20]. From 1970 to 1979 the incidence of severe ADRs per unit administered dextran 40 in Sweden was 0.013% [21]. We only have few informations about the GDR ADR rates, however in 1982 the rate of serious ADRs was estimated as being 0.011% increasing to 0.02% in 1984 [22]. The numerous ADRs lead to considerations whether the figures from GDR represented a real increase in reports in the GDR, given that reporting rates had increased temporarily due to previous under-reporting, or if there were specific problems with GDR products of dextrans [22]. An inspection carried out by IFAR at Serumwerk Bernburg in 1978 showed that only 50 % of dextran 40 and dextran 75 molecules were within the optimal range of molecule size, and high share of high number dextran molecules was suspected to have caused the reported ADRs [22]. In order to curb the increasing number of serious ADRs a new production method, partial fractionation, was introduced for dextran 75 in 1980, and the number of ADR reports declined [22]. In 1984 it was decided to introduce a new production technique for dextran 40, continuous fermentation, which was also used internationally, however due to lacking of financial resources and production orders at Serumwerk Bernburg the technique, could not be implemented until 1990 [23]. In 1985 import of dextran 1 (Promit) from Knoll AG in West Germany for restricted use in gynaecology was initiated as it was assumed that the injection of dextran 1 before dextran 40 could reduce the level of serious ADRs [24]. Due to limited production capacities of dextran 40 at Serumwerk Bernburg an additional import of dextran 40 from Sweden was necessary, however this dextran was reserved for use outside the health care sector, and due to the restricted availability of foreign currency the import could not be increased [25]. During the whole process IFAR never considered suspending the market authorization for dextran 40 as it was not possible for pharmacological reasons; gelatine was not a suitable substitute and hydroxyethyl starch was not available on the GDR market. Dextrans were used in severely ill patients to increase plasma volume and IFAR had to weigh between not delivering dextrans to the patients who need it resulting in many fatal cases, ore delivering dextrans with pharmaceutical quality problems possibly resulting in other cases of ADRs. Other examples of quality problems with production of pharmaceuticals in the GDR have also been identified [28]. In 1978 sterility problems in the production of Mydrum® (tropicamid) eye drops produced at the Ankerwerk in Rudolstadt were detected, and the contamination with pyrogens was due to problems with the bottle-washing machine. In order to solve the contamination problem it was suggested that the content of benzalconiumchlorid was increased of factor 20, rather than implementing a new machine that was in accordance with GMP standards [28]. Ampicillin for injection produced at Pharmachim was also contaminated with pyrogens, resulting in many ADR reports of skin reactions and increased temperature, however no information was found in the archive about which measures were implemented to tackle these problems [29].

ADRs reported for contrast media agents

For the contrast media agents' amidotrizoat and adipiodon a large number of allergic ADRs were reported, reactions that were already well known at that time and which were communicated to the GDR physicians through Medicamentum [26-27]. The large number of ADRs was not found to be related to pharmaceutical quality problems, and as the number of reports was comparable to international data, no further investigations were made.

System Organ Class	Adverse drug reaction (s)	N
Blood and lymphatic system disorders	Hemiparesis	6
	Thromboembophlebitis	2
Total		8
Cardiac disorder	Bradycardia	1
	Hypotoni	4
	Palpitation	1
	Tachycardia	10
	Cardiac condition	12
Total		28
Eye disorders	Conjunctivitis	1
	Eye pressure	6
	Ptosis eye lids	1
	Pupil dilatation	1
Total		9
Gastrointestinal disorder	Diarrhea	6
	Mouth swelling	10
	Nausea	50
	Vomiting	54
	Aphonia	1
	Lack of efficacy	1
	Stomach pain	4
Total		126
General disorders and administration site conditions	Dizziness	3
	Back pain	1
	Chills	12
	Dead	1
	Feeling uncomfortable	1
	Injection site reaction	14
	Aplasia	2
	Loss of consciouness	6
	Temperature changes	16
Total		56
Hepatobiliary disorders	Icterus	1
	Increase in transaminases	1
	Liver damage	1
		3
Immune system disorders	Anaphylactic schock/reaction	44
Total		44
Infection and infestations	Pyrogen reaction	1
Total		1
Injury, poisoning and procedural complications	Drug intolerance	2
Total		2
Investigations	Hypotoni	1
	Disturbance of heart rhytm	1
	Changes in blood pressure	17
	Pulse disturbances	6
Total		25
Musculoskeletal and connective tissue disorders	Muscle tremor	3
Total		3
Nervous system disorders	Convulsions	8
	Headache	2
	Hemiparesis	1
	Parasthesia	8
	Partial half-page syndrom	1
	Restlessness	2
	Somnolence	4
	Tremble	1
	Vertigo	6
Total		33

Psychiatric disorder	Apati	1
	Amnesia	1
	Anxiety	4
Total		6
Renal and urinary disorders	Kidney pain	1
	Oliguria	1
Total		2
Respiratory, thoracic and mediastinal disorders	Cyanosis	8
	Difficulty breathing	51
	Lung oedema	7
Total		66
Skin and subcutaneous disorders	Blister	23
	Erythema	5
	Exanthem	15
	Itching	2
	Oedema	33
	Skin redness	17
	Urticaria	44
Total		139
Vascular disorders	Circulatory collaps/schock	42
	Cerebral ischamie	1
Total		43
Total ADRs reported for amiotrizoat		594

Table 5: Characteristics of adverse drug reactions reported for amiotrizoat used as contrast media (ATC group V08AA01) in the German Democratic Republic, 1982 to 1990.

Strength and weaknesses of this study

The strength of this study is that it is the first which systematically has collected information about ADRs reported in the GDR. The included material comprised ADR reports collected over many years which varies in quality and length. The present work was based on documentary textual sources located in archives and elsewhere in Berlin and represents the authors' interpretations of the analyzed documents. The analysed material does not allow us to conclude if the GDR pharmaceutical industry in general was suffering from major problems with maintaining the pharmaceutical quality or if the pharmaceuticals were of lower quality than those produced in Western countries. In the dextran case correspondences between IFAR and Serumwerk Bernburg indicated that a high number of ADRs was reported in the GDR due to quality problems, but due to continuous lack of financial resources and equipment it was often not possible to improve the pharmaceutical quality sufficiently [30].

Conclusion

This study showed that the GDR spontaneous reporting systems were able to detect, in addition to its original purpose, pharmaceutical quality problems. This was further investigated for the production of dextrans. However, due to the lack of safer alternatives and foreign currency necessary to import purer products from Western countries, the products of lower quality could not be replaced easily.

Acknowledgement

Professor Dr. habil. Joachim Richter and Dr. Helmuth Koch, former Institut für Arzneimittelwesen, German Democratic Republic for their valuable information and advice during the research process and Ms Andrea Seitz, Wala Heilmittel GmbH for assistance with literature searches.

Funding

Lise Aagaard and Ulrich Meyer share first authorship of this article. This work was supported by the authors' place of work. No additional funding was received.

Contributors

L Aagaard, U Meyer, M Schaefer and EH Hansen designed the study, analysed data and wrote the first version of the manuscript. L Aagaard did the sampling. All authors saw and approved the final version of the manuscript.

Conflict of Interest Statement

We have no conflicts of interest to declare.

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