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Accidental Iatrogenic Intoxications by Cytotoxic Drugs

Error Analysis and Practical Preventive Strategies

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Abstract

Objectives: Drug errors are quite common. Many of them become harmful only if they remain undetected, ultimately resulting in injury to the patient. Errors with cytotoxic drugs are especially dangerous because of the highly toxic potential of the drugs involved. For medico-legal reasons, only 1 case of accidental iatrogenic intoxication by cytotoxic drugs tends to be investigated at a time, because the focus is placed on individual responsibility rather than on system errors. The aim of our study was to investigate whether accidental iatrogenic intoxications by cytotoxic drugs are faults of either the individual or the system. The statistical analysis of distribution and quality of such errors, and the in-depth analysis of contributing factors delivered a rational basis for the development of practical preventive strategies.

Methods: A total of 134 cases of accidental iatrogenic intoxication by a cytotoxic drug (from literature reports since 1966 identified by an electronic literature survey, as well as our own unpublished cases) underwent a systematic error analysis based on a 2-dimensional model of error generation. Incidents were classified by error characteristics and point in time of occurrence, and their distribution was statistically evaluated. The theories of error research, informatics, sensory physiology, cognitive psychology, occupational medicine and management have helped to classify and depict potential sources of error as well as reveal clues for error prevention.

Results: Monocausal errors were the exception. In the majority of cases, a confluence of unfavourable circumstances either brought about the error, or prevented its timely interception. Most cases with a fatal outcome involved erroneous drug administration. Object-inherent factors were the predominant causes. A lack of expert as well as general knowledge was a contributing element. In error detection and prevention of error sequelae, supervision and back-checking are essential. Improvement of both the individual training and work environment, enhanced object identification by manufacturers and hospitals, increased redundancy, proper usage of technical aids, and restructuring of systems are the hallmarks for error prevention.

Conclusions: Errors follow general patterns even in oncology. Complex inter-

dependencies of contributing factors are the rule. Thus, system changes of the working environment are most promising with regard to error prevention. Effective error control involves adapting a set of basic principles to the specific work environment. The work environment should allow for rectification of errors without penalty. Regular and ongoing intra-organisational error analysis needs to be an integral part of any error prevention strategy. However, it seems impossible to totally eliminate errors. Instead, if the environment guarantees timely error interception, most sequelae are avoided, and errors transform into a system-wide learning tool.

As present-day oncology continues to rely more and more on complex highly toxic drug regimens, accidental iatrogenic intoxications by cytotoxic drugs (AIICD) are increasingly becoming a problem.[1-94] Severe or lethal accidental iatrogenic intoxications are not restricted to cytotoxic drugs.[95,96] It is estimated that in the clinical setting, 1 medication error occurs each patient-day,[97] including dispensing errors (1 in 27 to 35 preparations,[98]) but excluding prescription errors (1 in 5 to 300 prescriptions).[99-101] Most of the errors carry no risk for the patient.

However, in a neonatal and paediatric intensive care unit, 1 in 5 medication associated errors put the patient at risk, or resulted in harm to the patient.[95] 20% of prescribing errors and a similar percentage of dispensing errors resulted in severe sequelae.[101] Due to their intrinsic toxic properties, cytotoxic drugs are particularly harmful if given in an overdose or improperly used. There are few antidotes available for this type of intoxication.

Drug errors have forensic,[1,4,13,60] economic,[97] personal,[102-104] and psychological consequences. In extreme cases, they give rise to suicide attempts by involved healthcare professionals.[105]

Between 1986 and 1995, three AIICD were observed in the paediatric oncology department at the University Children's Hospital, Bonn, Germany. In this paper we apply various aspects of modern research in the field of error research,[106-116] sensory physiology,[117,118] cognitive psychology,[119] communication research,[120-122] information science,[117,123] and management[124] to the analysis of our own unpublished case reports and other published case reports.[1-94] This approach has some limitations since only a minority of AIICD will be published in the medical literature. An observational study would have resulted in many more analysable errors.

Nevertheless, we choose this approach to generate data on system failures in various clinical settings and to appreciate the relative importance of individual antineoplastic drugs for severe AIICD. A second goal of this analysis was to prepare the development of sound and practicable preventive strategies.

Materials and Methods

Unpublished Case Reports

Case 1

At 1 year and 9 months of age, the patient was diagnosed with a testicular yolk sac tumour. He underwent unilateral orchidectomy. At 3 years 1 month of age, lung metastases developed. He was treated according to the German malignant testis tumours chemotherapy protocol. The first treatment day, he was scheduled to receive intravenous vinblastine 1.9mg (3 mg/m^2 body surface). The prescription was correct. But, a paediatric nurse with several years' experience as a hospital pharmacy technician prepared 9mg of vinblastine (15 mg/m^2) in a 10ml syringe instead of the requested 1.9mg. She incorrectly labelled the syringe '1.9mg vinblastine'. A medical doctor fully trained in paediatrics but still inexperienced in paediatric oncology administered the drug as prepared. However, before the patient showed any symptoms the physician recalled that vinblastine is usually given in a smaller volume using a smaller syringe. After checking the vial disposal container, the physician realised he had ad-

ministered an overdose. The child temporarily developed arterial hypertension that was responsive to nifedipine, accompanied by extreme restlessness.

Case 2

At 3 years and 7 months of age, the patient was diagnosed with acute lymphoblastic leukaemia. At 5 years and 9 months of age, 2 months after receiving chemotherapy (acute lymphoblastic leukaemia protocol – multicentre study of the BFM-group 1990) for 2 years, a CNS relapse was diagnosed, and cytotoxic treatment was started (relapse protocol in acute lymphoblastic leukaemia, multicentre study of the BFM-group 1990). On day 1 of the second treatment block he was scheduled to receive ifosfamide 400 mg/m^2. A correctly individualised dose of 300mg was prescribed. At the same time another patient was scheduled to receive 3000mg of ifosfamide. A senior nurse experienced in using cytotoxic drugs first prepared the 3000mg ifosfamide dose. She subsequently showed a trainee nurse how to prepare the 300mg dose. However, the experienced nurse again dispensed 3000mg ifosfamide instead of the prescribed 300mg, but she mislabelled the syringes as '300mg ifosfamide', as called for on the prescription. The incorrect ifosfamide infusion was started without being checked further by a physician. Three hours later a third nurse began to suspect a volume/dose mismatch, but as the syringes seemed to be correctly labelled with the prescribed dose, the correct patient's name, the right date, etc., she felt unsure. After trying unsuccessfully to contact the senior nurse by phone, she consulted the fellow, who in turn checked the disposal container and found only empty 1 and 2g ifosfamide vials. At this point, the patient's infusion came to an end. He showed abnormal fatigue for a short time followed by severe myelodepression.

Case 3

The patient was an 8-year-old boy with acute lymphoblastic leukaemia presented with CNS relapse. Single intrathecal doses of methotrexate 10mg and systemic cytotoxic therapy were scheduled. During the treatment course, an Ommaya reservoir was implanted to facilitate intrathecal methotrexate administration. Medical doctors and paramedical personnel were trained in the function and treatment indications for this device. Because of the risk of inducing leukoencephalopathy, the medical personnel were explicitly instructed that each single dose of methotrexate injected into the Ommaya reservoir should under no circumstances exceed 1mg. Intrathecal therapy was changed accordingly. The patient was scheduled to receive methotrexate 1mg in the reservoir twice daily for 3 consecutive days during each treatment cycle. These instructions were given orally, and not written down. A competent nurse, well experienced in paediatric oncology, who had attended the workshop on the Ommaya device, nonetheless prepared methotrexate 10mg for intrathecal use. This was administered by the junior resident. The patient then developed a headache for a short time. During

Table I. Stages of cytotoxic drug ordering and delivery (SDOD). Depending on institutional feasibilities, SDOD 1 to 4 are performed by members of different professions

SDOD	Profession	Result	Error group
Stage 1: prescribing	Physician	Medication order	Prescription error
Stage 2: volume calculation	Pharmacist	Dilution plan	Dispensing error
	Pharmacy technician		
	Nurse		
Stage 3: drug dispensing	Pharmacist	Cytotoxic drug, ready for administration	Dispensing error
	Pharmacy technician		
	Nurse		
	Physician		
Stage 4: administration according to mode of drug administration	Physician	Therapy	Application error
	Nurse		

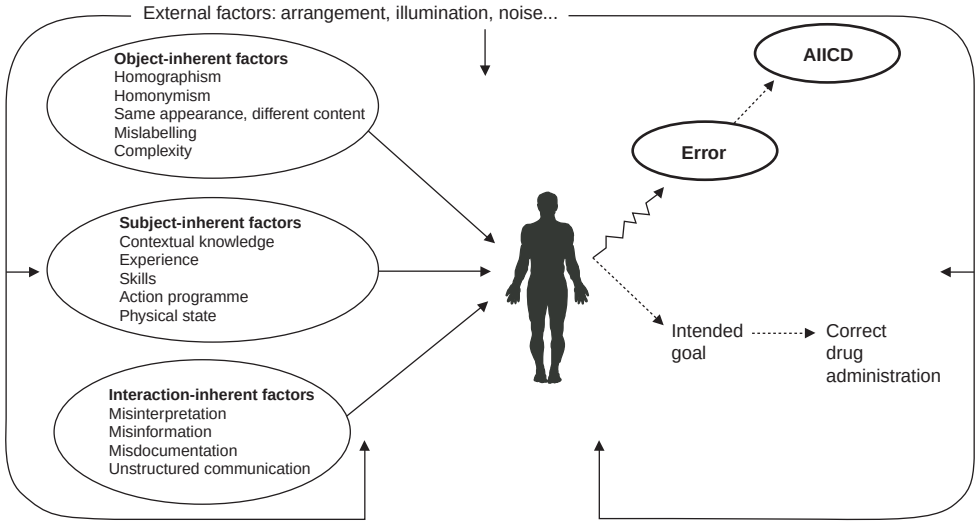

Fig. 1. Modelling error generation – impact of contributing factors. **AIICD** = Accidental iatrogenic intoxications by cytotoxic drugs.

the following daytime shift, when the nurse on duty reported that the patient had not yet received his intrathecal methotrexate 1mg dose for that morning, her colleague nurse who had prepared the previous 10mg dose realised her error.

Methods

Using Medline, International Pharmaceutical Abstracts and EMBASE, we ran a search for papers under the headings 'antineoplastic agents' and 'medication error' or 'drug overdose' or 'intoxication'. We limited our search to the publication years 1966 to March 1998. Any available paper referenced in the articles already found was included.

We defined a drug error as a prescription or medication error[97,125] leading to the incorrect administration of cytotoxic drugs, which in turn resulted in either a risk to health or intoxication. Injuries due to subcutaneous drug extravasation and intoxications from oral drugs were excluded from analysis.

We undertook an error analysis based on a 2-dimensional error model.

Error Analysis: Dimension 1

Dimension 1 is the point in time of the occurrence. Drug administration is the final step in a 4 working step sequence, termed the stages of drug ordering and delivery (SDOD), beginning with prescription (stage 1), followed by volume calculation (stage 2) and dispensing (stage 3) and ending with administration (stage 4) [table I]. Depending upon available human resources and/or hospital organisation, working steps 1 through 4 are carried out by different members of the professional staff. In each case, the error was systematically assigned to 1 or more of the 4 SDOD. If essential information on SDOD was missing, cases were excluded from this analysis.

Error Analysis: Dimension 2

Dimension 2 is the error characteristics and contributing factors. Causal factors leading to errors were classified according to a theoretical model (fig. 1). We distinguished between object-inherent, subject-inherent and interaction-inherent factors,[114] all of which may be affected by external factors (table II).[112,126]

The χ^2 test was applied where appropriate to test for independence and intergroup differences. A

contingency table was used to check for differences in item distribution.[127-129]

Results

Number of Cases

We analysed a total of 134 cases of AIICD (3 of our own and 131 from the literature) where the drugs were administered either intravenously or intrathecally. 63% of the cases of AIICD (62 out of 134) resulted in permanent injury, with some even resulting in death. 39% (52 out of 134) of the patients were ≤18 years old (table III).

Drugs Involved

In 73% of the cases either cisplatin, doxorubicin, methotrexate or vincristine was involved, leading to permanent injury or death in 52 cases (39%). These 4 drugs alone accounted for 84% of the cases with severe sequelae (table III).

Error Analysis: Dimension 1

There was a significantly larger number of AIICD-relevant errors in SDOD 3 and 4 (dispensing and administration) than in stage 1 (prescription) [table IV]. In comparison with cases where errors occurred exclusively during stages 1 to 3, cases of errors in stage 4 (drug administration) showed significantly more lethal sequelae (table IV).

Error Analysis: Dimension 2

The contingency table (table V) depicts significant differences in error distribution. Object-inherent errors clustered at SDOD 3 and 4, while interaction-inherent errors peaked at stage 2. In stage 1 and 4, subject-inherent factors predominated.

Error Detection

In several cases, including our group's, three unpublished case reports, errors were detected during or immediately following drug administration, and often before any symptoms developed.[3,5,8,12,13,18,20,23,31,45,52,53,55,57,60,64,67,75,78,94] Most papers fail to describe any circumstances leading to error detection.

Discussion

95 out of 134 of the AIICD were described in adequate detail for the purposes of error analysis. 66 errors could be traced to the first 3 SDOD. These 66 errors went undetected during 1 or more of the subsequent stages. Individual and institutional preventive strategies should therefore target minimising the error rate as well as improving error detection skills – the ultimate goal being prevention of adverse sequelae of errors.

Dimension 1

SDOD 1 (drug prescription), during which a standard treatment protocol is individualised for a specific patient, is especially prone to subject-in-

Table II. Accidental iatrogenic intoxications by cytotoxic drugs: classification of contributing factors and specific preventive measures

Category	Description	Preventive measure
Object-inherent	Due to intrinsic properties of the object (syringe, vial, etc.), different people tend to make similar errors	Insure product safety
Interaction-inherent	A spoken or written communication is misunderstood, or only partially transmitted. The problem may arise from signal transmission, or reception	Improve communication
Subject-inherent	Cause of error is closely related to the person involved and her/his skills. This category includes errors made by inexperienced or experienced staff. However, by definition these errors are not due to object or interaction-inherent factors	Improve quality control, education, supervision
External	Noise, poor lighting, visually confusing work environment, etc.	Optimise work environment

herent factors (table V). Contrary to our expectations, only a few AIICD arose from errors occurring at this stage (table IV). Most of these errors were discovered during the subsequent stages (SDOD 2 to 4) and adverse error consequences were thus forestalled.

Cytotoxic drugs are prepared anew each day. The daily dose in milligrams as prescribed is converted to an injection volume (millilitres). In most hospitals, SDOD 2 (drug-volume calculation) constitutes an interface between the medical and paramedical professions, i.e. pharmacist, pharmaceutical assistant or nurse (table I). Interaction-inherent factors predominate at this stage. 78% of errors occurring during the dilutional stage arose from inadequate communication.

SDOD 3, drug preparation, is almost always carried out by members of the paramedical professions, i.e. pharmacists and nursing staff. A lack of discrimination due to similar appearance of objects is the predominant object-inherent condition giving rise to errors at stage 3 (see below). 60% of all errors classified as object-inherent could be traced to this stage.

Table III. Accidental iatrogenic intoxications by intrathecal (IT) or intravenous (IV) cytotoxic drugs (AIICD) [cases published since 1966 plus 3 unpublished reports]

Drug	No. of AIICD			Reference
	total	fatal/severe[a]	age ≤18y	
IV dactinomycin (actinomycin D)	2	1	1	18, 60
IV decitabine (5-azacytidine)	1	0	1	89
IV cisplatin	13[b]	10	2	6, 14, 19, 23, 35, 38, 44, 56, 72, 74
IV cyclophosphamide	3	2	0	15, 51, 66, 77
IT cytarabine	1	0	1	53
IV cytarabine	2	0	0	7, 31
IT daunorubicin	1	1	1	67
IV doxorubicin	17	6	?[c]	4, 24, 27, 30, 51
IV liposomal doxorubicin	3	0	?[c]	28
IT doxorubicin	1	0	1	5
IV ifosfamide	1	0	0	Unpublished case report number 2[d]
IV interferon-α-2a	1	0	0	43
IV melphalan	4	1	1	20, 48
IV methotrexate	1	0	0	81
IT methotrexate	16	3	10	Unpublished case report number 3,[d] 2, 33, 34, 45, 46, 54, 58, 59, 65, 68, 79
IV mitoxantrone	4	0	1	42, 76
IV chlormethine (nitrogen mustard)	1	0	0	93
IV vinblastine	6	1	3	Unpublished case report number 1,[d] 17, 22, 29, 80, 91
IV vincristine	31	13	17	9-11, 13, 16, 18, 21, 25, 36, 41, 47, 50, 52, 62, 69, 82-88
IT vincristine	20	20	12	3, 8, 12, 13, 32, 39, 49, 55, 57, 63, 64, 73, 75, 78
IT vindesine	1	1	0	37
IV vindesine	1	1	1	71
IV vinorelbine	3	2	0	26, 61
All drugs	134	62	52	

a Fatal/severe = AIICD with a fatal outcome or resulting in permanent injury (level 5 or 6 according to Hartwig et al.[130]).

b Exact number of cases reported to Bristol Myers Oncology Division unknown.[70]

c Information on the age of 1 patient was not provided.

d See Materials and Methods.

In SDOD 1 to 3, errors can be checked following performance. However, due to the fact that SDOD 4 (drug administration) is an irreversible step, it is impossible to check for errors following performance, and more difficult to take preventive measures.

Errors in which an incorrect administration mode was chosen – such as intrathecal instead of intravenous injection – almost always have severe consequences.

Dimension 2

We identified object-, subject-, interaction-inherent and external factors that significantly contributed to an AIICD. Figure 1 illustrates this multicausality.

Object-Inherent Factors

When differentiation between objects is limited due to object-inherent characteristics (colour, labelling, dimensions, smell or texture) there exists an object-inherent danger to confuse them.

Vincristine and vinblastine, carboplatin and cisplatin, doxorubicin and daunorubicin are look-alike as well as sound-alike drugs. These object-inherent qualities render these drugs susceptible to confusion while being prescribed[10,23] and dispensed (unpublished case report number 1, see Materials and Methods).[6,10,19,23,27,38,62,70]

To date there have been 2 reports of lethal sequelae following mislabelling of intravenous drugs as intrathecal drugs.[67,90] In both cases, the inexperience of the physicians performing the lumbar puncture was probably a factor involved, as an experienced doctor would have noticed the lack of yellow in the methotrexate or the presence of red in the daunorubicin, which had been mixed up with cytarabine.[90] Both cases illustrate the need for more than a single security check,[1,131,132] particularly in situations where carrying out the preventive measures successfully requires precise technical knowledge. This is especially important, because cytotoxic drugs are not always administered by highly experienced personnel. In these 2 cases of fatal errors,[67,90] preventive measures failed. They were either too weak,[19] not strictly followed,[131] or in the worst case scenario, did not exist at all.

Table IV. Analysis of error distribution across stages of drug ordering and delivery (SDOD). Errors are assigned to 1 or several SDOD according to the information given in the case reports

SDOD	No. of errors	Lethal outcome[a]	Reference
1 (prescription)	16[b]	7	4, 10, 29, 50, 70, 76, 90, 77, 15, 21, 22, 23, 25
2 (calculation)	19	2	Unpublished case report number 1,[c] 10, 13, 17, 20, 30, 35, 44, 50, 51, 60, 70, 72, 86, 93
3 (dispensing)	31	7	Unpublished case reports numbers 2 and 3,[c] 6, 10, 16, 19, 23, 24, 26-28, 33, 38, 45, 52, 59, 62, 65, 67, 68, 70, 79, 87, 90
4 (administration)	31	17[d]	Unpublished case report number 3,[c] 3, 5, 8, 11-14, 18, 31-34, 39, 47, 49, 50, 53, 55, 57, 63, 64, 71, 73, 75, 78, 94
Assignation impossible	39	5	2, 7, 30, 36, 40-43, 46-48, 54, 56, 58, 61, 69, 74, 76, 80-85, 89, 92

a Lethal outcome = AIICD with lethal sequelae.

b Significantly fewer errors in SDOD 1 than in stages 3 and 4 ($p = 0.029$; χ^2 test).

c See Materials and Methods section.

d Proportion of AIICD with a lethal outcome is higher in stage 4 than in stages 1 to 3 ($p = 0.0024$; χ^2 test).

Complex treatment schedules can easily be misinterpreted. It is important to note that 85 AIICD occurred during polychemotherapy, (unpublished case reports numbers 1, 2 and 3, see Materials and Methods section)[2,3,5,8,10-15,16-21,27,30,33,37,39-42,44-55,57-59,62-64,67,68,72,73,48,49,78-85,87,89-94] and 4 AIICD involved more than 1 drug.[30,51]

Subject-Inherent Factors

Lack of contextual knowledge, experience and skills, impaired health conditions (i.e. fatigue) and decoupled action programmes are all subject-inherent cofactors that contribute significantly to errors. Decoupled action programmes are opera-

Table V. 4 × 3 contingency table, stage of drug ordering and delivery (SDOD) versus contributing factors

Contributing factor	SDOD			
	1 (prescription)	2 (calculation)	3 (dispensing)	4 (administration)
Object-inherent	2	0	26[a]	15[a]
Subject-inherent	11[b]	5	6	15[b]
Interaction-inherent	3	18[c]	1	0

a Errors associated with object-inherent factors predominate ($p < 0.001$; χ^2 test).
b Errors associated with subject-inherent factor predominate ($p \leq 0.01$; χ^2 test).
c Errors associated with interaction-inherent factors predominate ($p = 0.007$; χ^2 test).

tions which once successful are maintained under altered circumstances up to the point where this mode of action leads to an error.[114]

As documented by Lindahl,[60] a law suit involving an overdose of dactinomycin (actinomycin D) demonstrated that the drug was administered by a nurse who was not present when the spoken medical order was given or when the drug was dispensed by a second nurse. Because of lack of contextual knowledge, the administering nurse was unable to detect the medication error. Manelis[62] reported on a similar case.

14 AIICD occurred with inexperienced physicians (unpublished case report number 1, see Materials and Methods section).[5,13,36,40,46,50,55,57,88] In other cases, inexperience was presumably a contributing factor (e.g. a red coloured fluid was given intrathecally; or a translucent instead of a yellow fluid was administered.[5,39,63,67,86,87,90] Computational errors[11,13,29,41,42,44,46,50,59,60,61,70,76,86-88] that lead to prescribing of dosages beyond the upper limits cannot always be ascribed to a lack of experience. Moreover, in an era of ultra-high dose drug therapy and protocols containing peripheral stem cell support, upper dosage limits are on an upward curve.

Experience and error rate do not consistently correlate.[101,133] Certain types of medication errors tend to involve experienced as well as inexperienced staff. These errors, e.g. confusing of drug names, vials, labels or syringes usually occur when routine work is being carried out. Reports on aeronautical errors by Fitts and Jones[106] confirm this: instrument-reading errors were not restricted to any single class or group of pilots or to individuals at any particular level of experience.

It seems prudent to expect a decrease in the error rate at least in special error categories, provided prescriptions were written only by attending doctors. Such policy is incompatible with the hospital reality, and from the view of error research it is not even desirable. If junior doctors are not allowed to prescribe or administer cytotoxic drugs there is no room for personal development, resulting in a general loss of competence that finally endangers the patient.[113] When the prevention of the consequences of an error works only in cases where errors are totally eliminated, it is inevitable that such a prevention system will fail, since an integral part of being human is to make errors. Instead, error prevention should aim at active control of error consequences by rendering errors correctable and harmless, e.g. by triple checking by senior physician and pharmacists, etc. The result of checking processes must feed back to the person who made the error. By turning each error into a learning tool the error rate should decrease. By building such a 'safety net' error consequences should be prevented.[130,134]

It is not always a lack of concentration that causes decimal errors.[20,29,42,46,50,54,59,61,76,88,92,93] From our own experience we know that many doctors and paramedics are unfamiliar with decimals, strengths, calculation using the rule of 3, or weight and volume units.[4]

Routine work, i.e. if the acting person has internalised complex routine action sequences, is especially prone to errors.[107,110,113] If the demands change unexpectedly, the action sequence will continue unaltered, fail to meet the requirements, and deliver an inadequate result.[63,107,108] Our own case reports number 2 and 3 are classic examples.

Information is scarce on the acting person's physical condition. Only Brahams[13] and Lindahl[60] mention this point. Sleep deficiency,[13,135,136] working shifts,[136] physical exhaustion due to too high a workload,[60,135,137,138] and other conditions restricting physical well-being[139] contribute significantly to an increased error rate. According to Wehner,[115] in any action missing its goal there is an increased incompatibility between the acting person's task, the context and the cognitive composition of the acting person. This incompatibility is obvious in the case of the doctor who, after working nonstop for 30 hours, had to write a complex prescription and administer cytotoxic drugs unsupervised.[13]

Interaction-Inherent Factors

Impaired communication is a well known cause of medication errors.[97,137,140-142] According to Davis and Cohen[142] more than one-third of documented errors are caused by impaired communication.

Twelve AIICD resulted from reading ambiguously written prescriptions or from misunderstanding oral orders.[22-24,30,35,44,50,51,60,70,72,93] Misinterpretation of dosages given by the treatment protocol or by the prescription resulted in erroneous administration of weekly or total protocol doses on a daily basis.[13,15,21,30,35,40,44,50,51,66,70,72,77]

Some reports exist on multiple erroneous drug-doses administrations on successive days mainly due to misdocumentation.[13,14,18,47,50]

External Factors

External factors such as noise-stress, a visually confusing work environment and poor lighting[143] are conditions which contribute to medication errors.[139] In 1 study, a statistically significant relationship was identified between interruption, distraction, loudness of background noise and the dispensing error rate[144] while in another study, noise resulted in a decreased error rate.[145]

Under extreme external pressure, the error rate of experienced personnel increased by 5, while that of inexperienced personnel increases by 10.[112,146] The impact of contributing conditions of errors is enhanced under certain circumstances, for example: when under poor lighting an unclear label becomes illegible; when under noisy conditions a spoken order becomes ambiguous;[60] and when a lack of time impairs error detection.[63]

Multiple Errors

Although rarely described in detail, there seem to be specific factor constellations which favour AIICDs (fig. 1) [unpublished case reports numbers 1 and 3, see Materials and Methods section].[11,60,87] Two reports provide examples of situations in which object-inherent factors (similarity of syringes) provoked an error of an experienced staff member while the combination with a subject-inherent factor (inexperience of a second staff member) provoked the AIICD.[67,90]

Error Detection - the When and How

Many iatrogenic accidental intoxications by cytotoxic drugs escape detection until the patient becomes symptomatic,[49,85] which may take several days.[36,38] A striking number of AIICD, however, were detected even before the patient became symptomatic (unpublished case reports numbers 1, 2 and 3, see Materials and Methods section).[3,5,8,12,13,18,20,23,31,45,52,53,55,57,64,67,75,78,94] Shepherd et al.,[75] Bain et al.[8] and Slyter et al.[78] report that the error was detected while the lumbar puncture was still in progress. What is the mechanism which leads someone to the early detection of their own error?

While anticipating an action, we build up a mental goal intention[108] (comparable with a 'mental mirror image' of what we intend to do) which under normal circumstances is terminated just after having accomplished the goal. But if failing to achieve the goal would lead to grave consequences the termination process is delayed. After administering cytotoxic drugs, junior doctors commonly check the prescription or the waste repeatedly in order to reassure themselves. They do not finish their action (or terminate their goal intention) until they are convinced that their goal intention is realised and everything is alright.

Due to the delayed termination of the goal intention, the acting person is forced to repeatedly think through the entire action, and to compare his results to the goal intention step-by-step. In case of medication errors this often results in presymptomatic error detection.

Preventive Strategies

We have demonstrated that each stage of drug ordering and delivery has a preponderance of 1 or more specific error type (subject-, object-, interaction-inherent, externally determined). Thus, for optimal results the specific preventive strategy chosen should match the requirements of the specific SDOD. Furthermore, ideally prevention should target the members of those professions predominantly involved in that specific SDOD.

During drug prescription, preventive strategies should focus on techniques for avoiding computational errors[50,70,93] and confusion between similarly named drugs. During drug-volume calculation, the focus should be on interprofessional communication.[147] Since errors during drug preparation were mainly object-inherent – apart from structural changes made within the work environment – it is the manufacturers' responsibility to provide error-proof object identification.[98] During drug administration, most errors were subject- and object-inherent. Prevention should focus on improved object identification and training.

Tables VI and VII summarise the strategies to prevent AIICD.

Object-Inherent Factors

A significant number of errors resulted from drug homographism (look-alike) or homonymism (sound-alike). To prevent drug confusion, each prescription should give both the generic and trade name (table VII). This increases redundancy which in turn contributes to the reliability of communication.[119-123]

For example, a prescription that calls for 'Cisplatin (Carboplat™)' should alert the dispensing pharmacist or other staff members to the incompatibility of the 2 names.

Table VI. Strategies to prevent accidental iatrogenic intoxications by cytotoxic drugs (AIICD), grouped according to method and approach

A. Error prevention
1. Education/training
In-service training in the following:
Clinical pharmacology of anticancer drugs
Ward and hospital organisation (formulary system, documentation, communication, responsibilities, AIICD reporting system)
Form of prescription *lege artis*
Institution-specific error predominance
Institutional prevention policies and procedures
Canon of abbreviations
Mathematics and unit conversion
Patient: his/her own illness and treatment plan
Training modalities:
On-the-job training
Motivational training
Feedback session
Continual supervision
Updating of written guidelines
Videotapes
Case conferences on AIICD
2. Work environment
Blame-free communication about errors
Time management to reduce working hours and workload
Structured intra- and interprofessional communication (formulary systems, readable handwriting, exchange of information during change of shifts, etc.)
Minimising of interruptions
Sufficient personnel
3. Improved object identification
Pharmaceutical manufacturers:
Implicit coding
Auxiliary warning labels
Concentrations not graded in potencies of 10
Avoiding look-alikes and sound-alikes
Reasonable labelling (tradename and strength most important)
Size of vial according to milligram content not on volume content
Different connector types for each administration type (e.g. nasogastric tube, needle for lumbar puncture, needle for IV route)
Hospital:
Vials of fixed concentrations
One trade name per generic name per hospital
Auxiliary labelling
Separate storage according to route of administration
Prescription written per individual dose and only in milligrams
4. Redundancy
Prescription as generic and tradename, single dose absolute in milligrams and per m^2 body surface

Table VI. Contd

Consistent colour coding according to the route of administration
5. Hospital organisation
Unit dose distribution and control system
Satellite pharmacy
Continuous monitoring and analysis of errors
Continuous supervision of routine work by direct observation, anonymous self-reports, critical incident technique
Quality control assessment board
Standing hospital committee on safeguards
Compulsory institution specific preventive measures with double-check documentation
6. Technical devices
Prescription written with computer support, including plausibility check, and printout with standardised optical scheme
Computer based unit drug distribution system
B. Error recognition and prevention of error sequelae
Supervision and feedback:
At each stage of drug ordering and delivery
Especially of new staff members
Patient as his/her own control authority
C. Treatment of AIICD
Institution-specific emergency procedures for the first 5 critical minutes
Readily accessible information for quickly contacting on-call and on-duty staff as well as specialised support personnel from other institutions
On-site storage of antidotes

IV = intravenous.

There are vials on the market that are very similar in shape and volume but differ in their drug content by a factor of 5 to 10. For instance, 2ml vials of methotrexate may contain 5 or 50mg of substance, a fact which is reported to have caused AIICD.[45,79] The same problem exists with cytarabine (cytosine arabinoside) and vincristine.[16,52,87] Why, for example, is the latter produced in 5mg vials even though the highest recommended dose in any single injection is 2mg?[148] It is advisable to use only vials of the same strength for each generic drug (e.g. methotrexate, cytarabine). This establishes a linear relationship between dose and volume for each specific drug. It is also good practice to restrict the number of trade names to 1 for each single generic drug. Davis[149] suggested to stock cisplatin in liquid dosage forms and carboplatin in powder dosage forms.

Implicit coding (unfortunately rarely used by pharmaceutical manufacturers) is a type of packaging in which each concentration is assigned a particular vial shape, colour or size (e.g. round/angular, transparent/opaque, small/large) [second sensory modality].[121-123] Manufacturers who find this too costly could at a minimum correlate vial size with amount of drug, which would correspond to most user's subconscious and common sense expectations. Potency errors could be minimised if drugs were not packaged in potencies of 10.[142]

After calculation of drug dosage, drugs for each patient should be dispensed separately; for example, do not dispense vincristine for all patients, than methotrexate for all patients, etc. Before dispensing of drugs, syringe labels should be written according to the polychemotherapy prescription. Each drug should be dispensed separately and the label has to be attached immediately. While attaching labels to the ready-to-apply syringes, the content and number of labels and syringes should be cross-checked for each separate drug. Labels that vary in shape, colour, size, texture, etc., should be used for intravenous or intrathecal drugs.

As a preventive measure against erroneous object selection (vial, syringe, etc.) all cytotoxic drugs should be stored separately in different rooms, or cupboards etc., according to their intended mode of administration. When cytotoxic drugs are used simultaneously for intravenous and intrathecal administration in the same patient, it is advisable to prepare and administer them one after the other, and to administer the intravenous ones first and the intrathecal ones second.[53,75] Consistent colour-coding is essential.[150] We recommend that during all steps in the intravenous drug administration process a consistent colour-code be used (red is standard for intravenous). This includes prescriptions, syringe stoppers and plastic containers in which syringes and vials are stored.

During all steps in the intrathecal drug administration process a colour (for example, blue) should be used consistently. Syringes that have

been prepared for administration should be stored with empty vials in a blue plastic container. This container should not be kept near the intravenous medication.

Table VII. Basic formal requirements for minimising drug errors

A. Treatment protocol
1. Generic name
2. Dose in mg/m^2 body surface (or kg bodyweight)
3. Planned time of administration (treatment day, treatment hour)
4. Route of administration
5. Method of administration (bolus, infusion, light protected, etc.)
6. Supplementary information (dose strength, dilution and fluid/electrolyte requirements, sequence of administration in polychemotherapy, urine alkalisation, supportive medication, monitoring of drug levels, etc.)
B. Prescription
1-6. (See A. Treatment protocol)
7. Patient name, date of birth, bodyweight and height, body surface area
8. Generic and trade name of cytotoxic drug
9. Single dose, additionally in mg
10. Time of administration, additionally exact date and time of day
11. Mode of administration and exact fluid requirements
12. Supplementary information (exact timing of blood concentration monitoring, exact single dose of support medication, etc.)
13. Signature and name of prescriber including date and time
14. Signature and name of physician who checked the prescription, including date and time
C. Calculation of drug volume
1. Patient name and date of birth
2. Day of treatment, date, scheduled time of administration
3. Time of dispensing
4. Trade name
5. Single dose in mg
6. Calculation of the corresponding volume in ml according to actual strength used
7. Information on easy-to-check dilution steps
8. Route of administration
9. Mode of administration (bolus, infusion, etc.)
10. Name and signature of responsible person, including date and time
11. Name and signature of supervisor, including date and time
D. Prepared cytotoxic drug
1. Patient name, date of birth, identity number as bar-code
2. Date and time of dispensing
3. Name and strength of drug
4. Route of administration
5. Mode of administration
5. Auxiliary warning labels (i.e. 'for IV use only', colour coding)
6. Storage requirements

IV = intravenous.

Mix-ups of similar looking syringes have been reported not only in oncology but also in anaesthesiology. In two-thirds of the cases there was no mislabelling.[135] The problem of uniform syringes could be resolved using rough-textured coloured handles, and triangular or quadratic plungers instead of the conventional uniformly round ones. Such coding would allow for tactile discrimination. Intravenous and intrathecal syringe- and needle-connectors should be made mechanically incompatible.

A colour-check of the dispensed drug is crucial because red-coloured drugs (e.g. doxorubicin) can be lethal if administered intrathecally. Methotrexate should be held up against a light for a visual check. Its colour should match that of medium-concentrated urine.

An experienced nursing staff is important for error detecting in the last stage of cytotoxic drug administration. Consequently, all staff involved should have a good grasp of the basic principles of the pharmacology of cytotoxic drugs. However, this is not always the case due to the fact that in many hospitals interns and junior residents change wards every few weeks according to a rotation plan. A countervailing force to this lies in the fact that there is usually relatively little turnover in oncology nursing staff. Thus, the intuitive knowledge of cytotoxic drugs that nurses have acquired should allow them to detect errors, especially during lumbar punctures. A trained nurse should always be present during lumbar punctures even in the case of 2 or 3 physicians performing the procedure.[55]

As Kush et al.[151,152] reported, a preventive strategy involving the patients themselves could be semantic and pragmatic training. An important aspect of their project involved the use of optimally visualised treatment protocols that provide details on doses, drugs (e.g. colour, adverse effects, etc.), their timing and mode of administration as well as continuous patient information about their therapy progress.[153,154]

Computers are increasingly being used for error prevention in complex treatment protocols.[155-157] The numerous programmes currently on the market can easily handle almost any therapy protocol. The configured programme provides the complete prescription, including volume calculation, etc., after patient data (patient identification, date of birth, body surface, etc.) are entered.[155] Each piece of data is compared with internal standards and tested for plausibility and possible discrepancies. The programme also prints out labels for syringes and infusion bags. There are, however, a few minor problems with this software. For example, the data as they appear on the printout often are unsuitable for error prevention due to a lack of redundancy and clarity (e.g. lack of symbols, colours, tables). As with any complex newly marketed software the danger of internal bugs leading to systematic errors is always present. In the future, institution specific configurations, structured dialogues, colour prints and interactive error handling could all become suitable tools for minimising error rates and prevention of error sequelae.

Subject-Inherent Factors

Both medical and paramedical staff generally lack contextual knowledge.[99] A solution to this problem might be to have, for example, one staff pharmacist regularly accompanying physicians on ward rounds. This would enable him or her to achieve specific patient-related knowledge.[134,158] No one would dispute the necessity for nursing staff to receive full and complete patient data. The type of information to be exchanged and the order in which it is to be exchanged should be structured. These mechanisms have proven to be effective in decreasing time-shift related error rate.[138] The broadening of the knowledge base of the ward's entire staff could be a first step towards establishing a system to detect and prevent as yet unknown and undocumented error mechanisms.

Staff experience and expertise are major determinants of drug safety. For error prevention, each junior resident should be trained in common error sources, specific to cytotoxic treatment. Continuous on-the-job training is essential not only for junior residents but for all staff members.

In order to increase redundancy[119-123] of the prescription, the total drug amount (mg) as well as the specific amount (mg/kg bodyweight), or the amount proportionate to body surface (mg/m^2 body surface) are given. Alternatively, standardised forms should be used (table IV).[159,160] These measures should help in detection of erroneous calculations.[29,42,50,69,76,88,91,93]

A lack of skills may lead to the incorrect dose or faulty mode of administration. For prevention we suggest that in treatment protocols, all doses of cytotoxic drugs should be strictly given in milligram units. In doing so, there is no need to convert from grams into milligrams and micrograms – units that are aurally and visually similar.

Any setting with a great deal of routine work is prone to errors from decoupled action programmes,[107,108,115] e.g. when a normally adequate sequence of actions is performed under altered circumstances, thus provoking inadequate results. Having an independent staff member compare the goal and the result of each step of the action sequence is a powerful preventive tool.

Finally, working on an oncological ward is time-consuming, challenging, and emotionally demanding.[115,124,161] Careful supervision, acknowledgement by other staff members, and sufficient time dedicated to recreation are all essential for preventing exhaustion and burn-out.

Interaction-Inherent Factors

To avoid ambiguity and false interpretation only written orders should be used and abbreviation should not be used. In addition, all written prescriptions should include a minimum amount of information (table VII). The single dose (not the total daily or total protocol dose) should be given. To ensure the legibility of the prescription it is strongly advisable to write clearly, preferably in block letters. Whenever feasible, forms should be provided with the scheduled dose referenced to body surface, as given in the treatment protocol. Computer systems are an alternative.[155]

To compensate for the different backgrounds and communication styles of various professions (e.g. physician and pharmacist), each calculation should be given in written form and checked by an independent colleague (either doctor or pharmacist). If this is done, errors such as overlooking or misplacing a decimal point or a number[11,50,86,92,162] have a better chance of being detected early. From our own experience we strongly recommend using a calculator even for seemingly simple calculations.

Each drug administration must be immediately documented in the chart. We recommend using form sheets which visually display the chemotherapy protocol and also contain the written prescription.

External Factors

Writing a prescription is one of the oncologist's most demanding tasks. It is the hospital's responsibility to provide a quiet working place, and it is the duty of the department head to provide the necessary amount of time to do the task properly.

The pharmacist's drug dispensing work area should match the common safety standards and be an integral part of the oncological ward (satellite pharmacy). High lighting intensity in the pharmacy reduces the error rate significantly.[143]

The doctor primarily responsible for the patient should administer all intrathecal drugs under stress-free conditions in an area exclusively reserved for this procedure.

The hallmarks of error detection are supervision and checking. The specific knowledge about the handling of cytotoxic drugs should be transmitted or reactivated while the action steps are being carried out under experienced supervision. Moreover, supervision stimulates the acting person to consciously break down his goal intention into single steps in order to detect any mismatch to the current, particular situation.[107,108]

Every intercepted error should be documented anonymously and discussed during regular meetings in order to discover system failures before errors lead to intoxications.

Synopsis of Preventive Strategies

Only the most important principles of error control are listed in table VI.[1,49,97,99,101,104,105,132,134,137,139,140,142,156,158,159,163,164] Establishing effective error control means adapting general principles to the specific working environment. This involves seeking not only expert advice but also local experience. Experienced staff members have the diagnostic competence in system failure detection which could be mobilised by the creation of a local proposal board.[113] It is undisputed that the creative integration of personnel increases compliance in error prevention guidelines. According to Byrd[96] 80% of all medication errors are based on noncompliance with guidelines.

It is of utmost importance that the working environment allows staff to correct their errors without placing them in a conflict of roles. Peer pressure to conform is counterproductive to timely error detection and correction.[147]

In some cases an early therapy is effective in preventing harmful sequelae.[79,165-168] At all times, each ward should have suitable antidotes readily available as well as treatment schedules detailed enough to help in the immediate establishment of an efficient therapy.[168,164] The rapid implementation of the correct measures can be lifesaving,[2,79] but the rapid implementation of incorrect measures can be fatal.[169] Information on recommended management of AIICD are also available through the internet at: http://www.coast.net/SimTel/msdos/science.html.

Conclusions

System failure errors require system changes. The hallmarks for error prevention are: (i) improvement in training and the working environment; (ii) improved object identification by industry and hospitals; (iii) increased redundancy; (iv) proper use of technical aids; and (v) structural system changes. Proper checking and supervision are essential. To a substantial degree the individual working environment dictates error-prone conditions. Thus, expertise from local medical doctors,

nurses, paramedics and administrators should be sought. They should be assigned members of a local safety board. Total error prevention is unrealistic. Instead, the realistic, achievable goal is to allow for the correction of errors in order to prevent severe sequelae. By doing so, errors become system-wide learning tools.

In our study we have been able to depict the multicausality of most accidental intoxications by cytotoxic drugs. Thus, individual blame is unrealistic and unjust. We restrain from personal judgement, citing instead Wehner:[139]

> *It is not the fault of those people who in the end actually made the mistake. It is rather the fault of all those who were involved in the planning, the technical support, the controlling and the judging of a scenario which all together is impossible to handle individually.*

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