SHORT COMMUNICATION

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Deriving Dose Limits for Warnings in Electronic Prescribing Systems

Statistical Analysis of Prescription Data at University Hospital Birmingham, UK

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Abstract

Introduction: Electronic decision support can reduce medication errors, and dose-range checking is one element of that support.

Objective: The aim of this study was to design an approach to setting upper dose warning limits in electronic prescribing systems where there are historical data on dosing.

Method: We used historical data on 56 drug-form combinations for which over 100 prescriptions had been issued between 1 June 2009 and 31 May 2010 in a bespoke electronic prescribing system at University Hospital Birmingham, UK. First, two experts derived dose limits for each drug-form combination, then the drugs were randomly divided into a training set and a test set. A variation of the 'Nearest Rank' approach to estimate statistical limits was used to derive the percentile with the optimal sensitivity and specificity.

Results: For the 28 drug-form combinations in the test set, the 86th percentile of dose gave a mean sensitivity of 95.3% and a mean specificity of 97.9% for warning limits, representing the highest reasonable dose; the 96th percentile gave a mean sensitivity of 90.2% and mean specificity of 99.5% for disallow limits, beyond which no dose should be prescribed.

Conclusions: Dosing decision support within electronic prescribing systems can be derived by statistical analysis of historical prescription data. We advocate a combined theoretical and statistical derivation of dose checking rules in order to ensure that prescribers are alerted appropriately to potentially toxic doses.

Introduction

Clinical decision support (CDS) tools within electronic prescribing systems (Computerized Physician Order Entry) can reduce medication errors when they alert the prescriber to specific patient- and drug-related factors.[1] Major aspects of CDS include drug-disease contraindications,

drug-drug interactions and dose range checking. We have previously suggested that pharmacological knowledge can allow rules to be designed in order to provide drug-disease contraindication warnings.[2]

In the same way, it is possible to derive sensible alerts to warn that prescribed doses are potentially unsafe, and to prevent the prescription of obviously unsafe doses. Here we consider another approach to the problem of unsafe dosing where electronic prescribing systems have been in use long enough to provide historical data on dosing.

Statistical Process Control (SPC) is a technique to ensure that 'processes' – originally engineering manufacturing processes – remain within acceptable limits. SPC permits deviations from expected values to be divided into random variation within the production process – 'normal cause variation', and systematic deviation in a process that is out of control – 'special cause variation.'[3] We have previously considered the application of these methods to the treatment of patients in various healthcare and patient settings.[4] By using a concept akin to special cause variation and applying it to dosing for a wide range of medicines, we examined the feasibility of using statistical methods to derive sensible dosing limits from electronic prescribing data.

Dosing limits for many drugs are well defined, and we first established acceptable limits by using a quasi-Delphi exercise with two physician experts. This allowed us to compare statistical results with 'expert' opinion.

Method

We extracted information on the 100 most frequent medication orders in the period 1 June 2009 to 31 May 2010 from a locally-developed bespoke electronic prescribing system with a comprehensive audit database at University Hospital Birmingham. We have described both the system and the University hospital previously.[5] For these medicines we extracted all drug-form combinations. We excluded any drugs where the system already had maximum dosing limits, as such limits constrain the dose range at ordering and thus affect the distribution of prescribed doses. We also excluded drug-form combinations for which fewer than 100 prescriptions had been completed. This number was chosen so that we could be reasonably sure that the dose distribution would be established and so that every integer percentile from 1 to 100 would be associated with a different prescription (see below). For completeness we included medicines that met these criteria even if the risk of overdose was not considered to be high (e.g. topical applications, graduated elastic stockings). Two physicians with expertise in clinical pharmacology (REF and JJC) examined all drug-form combinations, and consulted the Summary of Product Characteristics[6] and the British National Formulary[7] to develop theoretical 'warning' and 'disallow' limits for these medicines. The warning limit represented the largest single dose of each drug that would, in the view of the experts, reasonably be prescribed. Attempts to prescribe doses greater than this would generate a warning message, encouraging the prescriber to verify the requested dose. The disallow limit was set at the maximum dose allowable in any circumstance. Prescriptions for doses greater than this would come to a 'hard-stop', where the prescriber would not be permitted to continue. We did not consider contraindications or demographic or co-morbid factors that would influence dose limits in individual patients.

For each drug-form combination, the number of prescribed doses that were above these limits was established. This information was then fed back to the experts in the manner of a quasi-Delphi exercise, to give an opportunity to amend any of the limits that appeared to be excessively lenient or restrictive. The process was repeated until the experts were satisfied that the limits were reasonable. A statistician independent of the investigation (Peter G. Nightingale) then randomly divided the drug-form combinations into two sets – one on which to develop a method of limit prediction (training set) and the other on which to test the method (test set).

Since we knew that distributions of doses tend to be highly skewed, we used a non-parametric approach. The values of all integer percentiles from 0 to 100 were generated for each of the drug-form combinations in the training set. After various

methods were explored, we settled on a variation on the 'Nearest Rank' approach to estimate statistical limits.[8] In this approach we used the N^{th} percentile to define a dose (D) such that N% of prescriptions were for doses that did not exceed D. The drug-form combinations were then considered individually. The sensitivity (a measure of the extent to which doses that are *unreasonable* generate warnings) and specificity (a measure of the extent to which doses that are *reasonable* do not generate warnings) of each percentile was calculated, with the 'gold standard' being the refined expert warning limits.

In order to give an overall indicator of the ability of the percentiles to detect excessive doses, the unweighted mean sensitivity and specificity for each percentile was calculated across the remaining drug forms in the training set. The resulting set of statistics was then used to create a receiver operating characteristic (ROC) curve to test the usefulness of using percentiles to estimate dose limits. The sensitivities and specificities were then analysed in more detail, in order to determine the best percentile to use as a dose limit. The sensitivities and specificities associated with the use of a range of percentiles were plotted. These plots were interrogated to select the percentile which corresponded to the optimum combination of sensitivity and specificity, and hence would be the best to use as a dose limit. Once this decision had been made, the chosen limit was applied to the data in the test set in order to validate the accuracy of classification.

The whole process was then repeated to produce a predictor for the disallow limit.

Results

There were 120 valid drug-form combinations for the 100 most frequently prescribed drugs. Of these combinations, fewer than 100 prescriptions had been completed for 57 combinations, leaving 63 combinations for analysis.

Expert Limits

The clinical pharmacologists examined the 63 drug-form combinations and were able to estimate warning and disallow limits for 56 of these. The seven drug forms for which they found it impossible to define dose limits were various infusion forms of fentanyl, alfentanil, bupivacaine and propofol. After the first iteration, the clinical pharmacologists were satisfied that they had defined reasonable warning and disallow limits for 45 out of 56 drug-form combinations; after a second iteration they had defined satisfactory limits for the remainder. The 56 drug-form combinations were randomized into two sets of 28 for the statistical analyses.

Warning Limit

The mean sensitivity and specificity of the percentiles as predictors of the warning limit were calculated across all of the drug forms in the training set. Where none of the prescriptions exceeded the dose limits set by the experts, the sensitivities were incalculable; however, the specificities were still used. The results were displayed on an ROC curve (figure 1). The area under the curve (AUC) was 99.4%.

The plot in figure 2 was then created to determine which of the percentiles provided the best

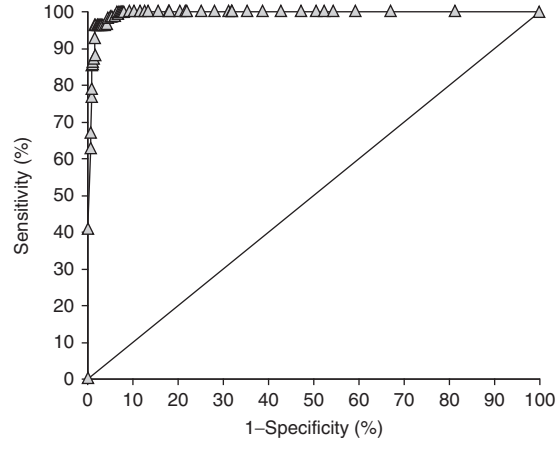

Fig. 1. ROC curve of the mean sensitivity and specificity of the integer percentiles 0–100 in predicting 'gold standard' warning limits set by the experts. The values are unweighted means across the drugs in the training set. Drugs where the sensitivity was incalculable were excluded from the calculation of mean sensitivity, but were considered in the calculation of mean specificity. The area under the curve was 99.4%. **ROC** = receiver operating characteristic.

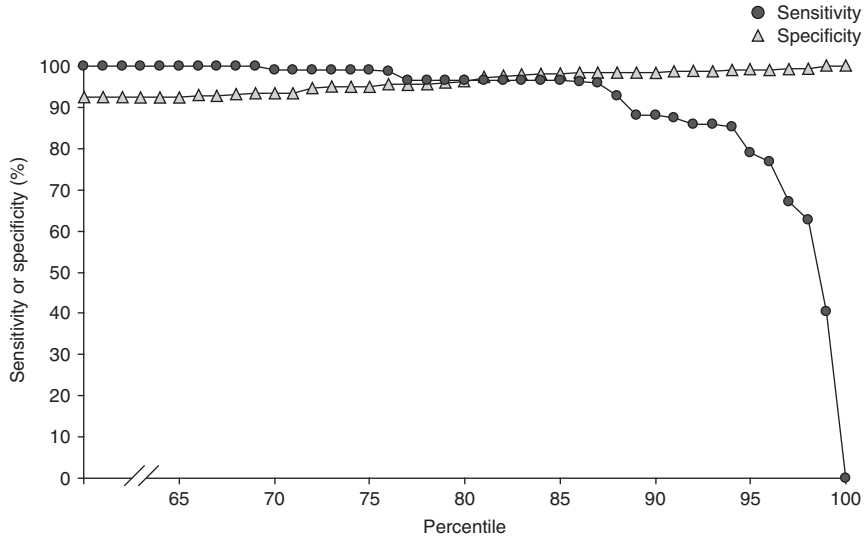

Fig. 2. The mean sensitivity and specificity of the integer percentiles 0–100, with the 'gold standard' being the warning limits set by the experts. The values are unweighted means across the drugs in the training set. Drugs where the sensitivity was incalculable were excluded from the calculation of mean sensitivity, but were considered in the calculation of mean specificity.

estimate of the expert-derived 'gold standards'. This plot shows the mean sensitivity and specificity for a range of percentiles that could reasonably be used as predictors of the warning limit. The 86th percentile was chosen from this information to be the optimal predictor of this limit; it has high mean specificity (98.5%). It also has a high mean sensitivity (96.4%), which falls sharply over the subsequent percentiles. Table I displays the sensitivity and specificity values for the individual drug forms in the training set, as well as the limits proposed by both the experts and the 86th percentile. In the vast majority of drug forms, both the sensitivity and specificity are in excess of 90%, with 15 drug forms having values of 100% for both statistics. The only outlying drug form was hydrocortisone tablets, with a sensitivity of 29.4%.

In order to verify the accuracy of the chosen predictor of the warning limit, the sensitivity and specificity of the 86th percentile were recalculated using the drug forms in the test set. This resulted in a mean sensitivity of 95.3% and a mean specificity of 97.9%, suggesting that the accuracy calculated previously describes the predictor when it is applied to new drug forms. Table II details the sensitivity and specificity of the individual drug forms in the test set. As before, the majority of drug forms had values for both statistics in excess of 90% (n = 14). The only outlying drug form was the omeprazole infusion, with a sensitivity of 10.6%.

Disallow Limit

The area under the ROC curve (figure 3) for the estimation of the disallow limit in the training set was 99.7%. Figure 4 displays the relationship between the mean sensitivity, specificity and the percentile used as a predictor. The sensitivity remains at 100% until the 96th percentile, after which it begins to fall dramatically. Hence, it was concluded that the 96th percentile was the optimal predictor of the expert disallow limit, with a mean sensitivity of 100%, and mean specificity of 98.7%.

The statistics for individual drug forms are detailed in table I. For all drug forms where a sensitivity value was calculable, the resulting statistic was 100%. Other than for haloperidol enteric-coated tablet (specificity = 84.1%), the drug forms in the training set had specificity values in excess of 95%.

These statistics were then recalculated using the data from the test set as a form of validation.

Table I. Details for all drug forms in the training set

Drug information				Warning limit				Disallow limit			
Drug name	Form	Units[a]	No. of scripts	Expert limit	86th percentile	Sensitivity[b] (%)	Specificity (%)	Expert limit	96th percentile	Sensitivity[b] (%)	Specificity (%)
Human recombinant Soluble Insulin (Actrapid®, Novo Nordisk) standard sliding scale	Drug infusion	units	2769	72	50	NA	100.0	288	50	NA	100.00
Colecalciferol with Calcium (Adcal-D_3®, ProStrakan)	Tablet	Tablet	3130	2	2	100.0	100.0	2	2	100.00	100.00
Aspirin	Suppository	mg	676	300	300	NA	100.0	600	300	NA	100.00
Aspirin	EC tablet	mg	192	600	75	NA	94.3	900	150	NA	97.40
Chlordiazepoxide	Capsule	mg	3550	40	30	100.0	95.7	60	60	100.00	100.00
Chlorhexidine 4% topical solution	Solution	Application	6705	1	1	NA	100.0	2	1	NA	100.00
Clopidogrel	Tablet	mg	5591	300	300	100.0	100.0	900	300	NA	96.01
Co-amoxiclav	Suspension	mg	196	625	625	100.0	100.0	625	625	100.00	100.00
Dexamethasone	Tablet	mg	5419	8	8	100.0	100.0	20	8	100.00	97.37
Dexamethasone	Oral solution	mg	140	8	8	100.0	100.0	16	11	NA	96.43
Diclofenac	Injection	mg	476	75	75	100.0	100.0	75	75	100.00	100.00
Esomeprazole	Injection	mg	2537	40	40	100.0	100.0	40	40	100.00	100.00
Fentanyl	Injection	μg	131	100	125	94.7	100.0	200	200	100.00	100.00
Fortisip bottle (Nutricia)	Liquid	mL	4160	200	200	100.0	100.0	400	200	100.00	99.86
Gabapentin	Capsule	mg	2049	800	600	100.0	98.6	1200	1200	100.00	100.00
Nitroglycerin	Drug infusion	mg	1397	144	50	NA	100.0	288	50	NA	100.00
Haloperidol	EC tablet	mg	446	10	5	NA	84.1	15	5	NA	84.08
Hydrocortisone	Tablet	mg	742	30	50	29.4	100.0	160	100	100.00	100.00
Ibuprofen	Suspension	mg	115	400	400	100.0	100.0	600	400	NA	99.13
Ipratropium bromide	Nebulizer	μg	2678	2000	500	NA	100.0	2000	500	NA	100.00
Metoclopramide	Syrup	mg	103	10	10	100.0	100.0	20	20	NA	100.00
Midazolam	Injection	mg	1946	10	5	100.0	92.3	30	9	NA	96.15
Ondansetron	Injection	mg	8298	8	8	100.0	100.0	8	8	100.00	100.00
Phosphate enema	Enema	Enema	3856	1	1	100.0	100.0	1	1	100.00	100.00
Prednisolone	EC tablet	mg	129	40	40	100.0	100.0	60	60	100.00	100.00
Potassium chloride effervescent tablets (Sando-K®, HK Pharma)	Disp. tablet	Tablet	8484	2	2	100.0	100.0	4	2	100.00	98.14
Simple linctus, BP	Liquid	mL	1913	10	5	100.0	93.7	10	10	100.00	100.00
Vancomycin	Infusion	g	844	1	1	100.0	100.0	1.5	1	100.00	98.22

a For dose forms tablet and enema, units of doses are given per single unit dose (e.g. one enema).

b Sensitivity values where none of the prescriptions exceeded the expert dose limits are omitted as they are incalculable.

BP = British Pharmacopoeia; **Disp.** = dispersible; **EC** = enteric-coated; **NA** = not applicable.

Table II. Details for all drug forms in the test set

Drug information				Warning limit				Disallow limit			
Drug name	Form	Units[a]	No. of scripts	Expert limit	86th percentile	Sensitivity[b] (%)	Specificity (%)	Expert limit	96th percentile	Sensitivity[b] (%)	Specificity (%)
Amiodarone	Infusion	mg	209	1200	900	NA	99.5	1200	900	NA	99.52
Aspirin	Disp. tablet	mg	14567	600	300	100.0	99.9	900	300	NA	99.90
Bisoprolol	Tablet	mg	5323	10	5	100.0	89.4	10	10	100.00	100.00
Cyclizine	Graseby	mg	1607	150	150	NA	100.0	150	150	NA	100.00
Diazepam	Rectal tubes	mg	156	10	10	100.0	100.0	20	10	100.00	98.06
Diclofenac	Gel	Application	203	1	1	100.0	100.0	1	1	100.00	100.00
Furosemide	Infusion	mg	529	250	250	100.0	100.0	1000	500	NA	100.00
Scopolamine butylbromide	EC tablet	mg	479	120	80	100.0	88.4	120	120	100.00	100.00
Lactulose	Oral solution	mL	8183	30	15	100.0	88.5	50	20	100.00	97.51
Magnesium sulfate 50%	Infusion	mmol	2389	96	20	NA	100.0	96	20	NA	100.00
Magnesium sulfate 50%	Additive	mmol	1474	20	20	100.0	100.0	20	30	12.41	100.00
Magnesium sulfate 50%	Injection	mmol	180	20	20	NA	100.0	20	20	NA	100.00
Meropenem	Injection	g	5377	1	1	100.0	100.0	2	2	100.00	100.00
Metoclopramide	Graseby	mg	277	50	40	100.0	96.9	100	60	NA	100.00
Midazolam	Graseby	mg	625	50	20	NA	96.3	100	20	NA	96.32
Morphine PCA	Infusion	mg	2678	120	100	NA	100.0	250	100	NA	100.00
Morphine SR	Capsule	mg	2419	100	70	100.0	93.5	200	140	100.00	97.86
Mupirocin 2%	Ointment	Application	6427	3	1	NA	100.0	3	1	NA	100.00
Omeprazole	Infusion	mg	124	40	80	10.6	100.0	80	96	60.00	100.00
Omeprazole	Injection	mg	110	40	40	100.0	100.0	80	80	NA	100.00
Ondansetron	Tablet	mg	2711	8	8	100.0	100.0	16	8	NA	99.78
Potassium chloride 15% (neat)	Infusion	mmol	3542	120	120	NA	100.0	240	120	NA	100.00
Tacrolimus (Prograf®, Astellas)	Capsule	mg	2450	15	8	100.0	88.7	15	14	100.00	99.50
0.9% Sodium chloride nebulizer	Nebulizer	mL	3194	5	5	100.0	100.0	5	5	100.00	100.00
Senna	Liquid	mL	1691	20	10	100.0	93.7	20	20	100.00	100.00
T.E.D.S.® compression stockings	Hosiery	Stockings	12483	2	2	NA	100.0	2	2	NA	100.00
Warfarin	Tablet	mg	2141	10	10	100.0	100.0	20	10	NA	98.65
Vitamins B and C	Injection	Ampoule	2009	4	4	100.0	100.0	4	4	100.00	100.00

a For dose forms ampoule and application, units of doses are given per single unit dose (e.g. per ampoule).

b Sensitivity values where none of the prescriptions exceeded the expert dose limits are omitted, as they are incalculable.

Disp. = dispersible; **EC** = enteric-coated; **NA** = not applicable; **PCA** = patient controlled analgesia; **SR** = sustained release.

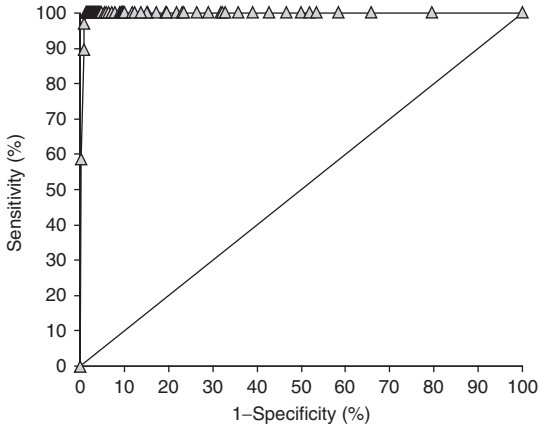

Fig. 3. ROC curve of the mean sensitivity and specificity of the integer percentiles 0–100 in predicting 'gold standard' disallow limits set by the experts. The values are unweighted means across 16 drugs in the training set. The remaining 12 drugs in the set were excluded as no prescriptions exceeded the limits set by the experts, making the sensitivity incalculable. The area under the curve was 99.7%. **ROC** = receiver operating characteristic.

This resulted in a mean sensitivity of 90.2%, and mean specificity of 99.5%. The results for the individual drug forms in this set (table II) revealed that all of the specificity statistics were greater than 95%. The calculable sensitivity values were also generally high, with the statistics for the majority of drug forms being 100% (n = 10). The drug forms with lower levels of sensitivity were magnesium sulfate 50% additive (sensitivity = 12.4%) and omeprazole infusion (sensitivity = 60.0%).

Discussion

We have shown that the statistical analysis of data from an electronic prescribing system can be used to define sensible limits for dosing decision support over a wide range of commonly prescribed drugs. The limits chosen by the experts did not always accord with current practice in the hospital. This lack of accord can be resolved by discussion between clinicians.

Basing dosing rules on statistical analysis of 'usual' doses has several potential benefits. Specific local protocols or specialty-specific practice is incorporated into dose limits derived from analysis of 'usual' doses in the locality or area. Assuming that enough prescriptions have been issued, one is relatively reassured that dose limits derived in this manner fit with accepted practice. We believe that prescribers are more likely to accept alerts if they are known to be based on

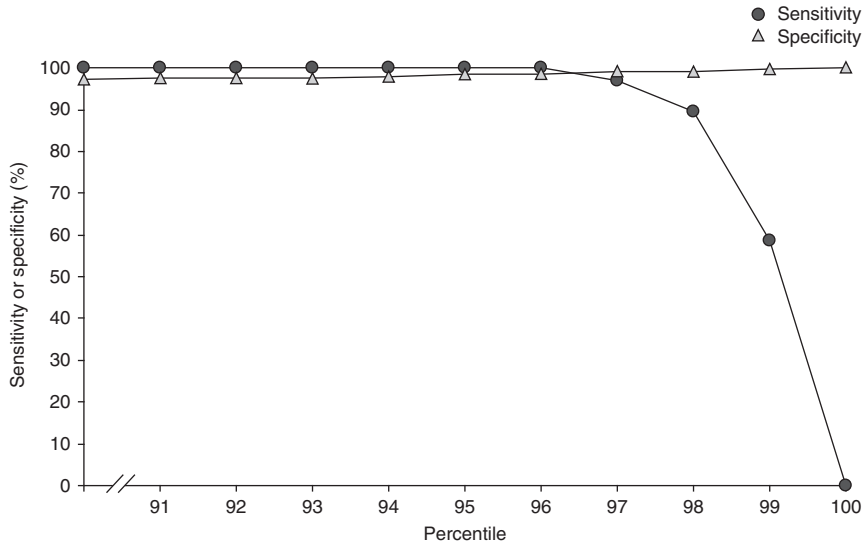

Fig. 4. The mean sensitivity and specificity of the integer percentiles 0–100, with the 'gold standard' being the disallow limits set by the experts. The values are unweighted means of the drugs in the training set.

local practice and give information about dosing related to specific prescribing systems.

The reasons for outliers seem to differ for different medicines. The experts probably assessed the dosing of magnesium sulfate inaccurately because it is ill-defined. High-dose hydrocortisone tablets are used in some services in place of prednisolone. Intravenous omeprazole always seems to be used at maximal dose. When these and other unusual dosing strategies are uncovered, they could usefully prompt consultation with 'outlier' users, and negotiation to determine best – or at least acceptable – practice.

This statistical approach only works if there are sufficient data. Where few prescriptions are issued for a certain drug-form combination, then statistical derivation is not possible. If dose limit warnings are applied in clinical situations very different from those in which the derivation set was obtained, for example in particularly underweight or frail elderly patients, the system may fail to warn of a dose that is potentially toxic in the circumstances.

Statistical limits derived from one set of clinical practices may need to be altered when practice changes (for example when a new dosing schedule is introduced).

The use of 'approved' dosing information from manufacturers' information sources can generate many alerts. This brings with it the danger of 'alert fatigue.'[9] We expect statistically-based warnings to generate more clinically appropriate alerts, although we are aware of the possible danger that poor clinical practice will become institutionalized. A combination of statistical and theoretical knowledge is likely to be the most appropriate way of ensuring that dosing rules are suitable for any given situation.

Conclusions

Dosing decision support within electronic prescribing systems can be derived by statistical analysis of historical prescription data. This should allow individual organizations and system providers to efficiently build up knowledge about appropriate dose limits. We present the results from such a statistical analysis on drugs for which dose limits had not previously been set. We advocate a combined theoretical and statistical derivation of dose checking rules in order to ensure that prescribers are alerted appropriately to potentially toxic doses.

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