Mass flows of X-ray contrast media and cytostatics in hospital wastewater

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Abstract

Little is known about the significance of hospitals as point sources for the
emission of organic micropollutants into the aquatic environment. A mass flow analysis
of pharmaceuticals and diagnostics used in hospitals was performed on the site of a
representative Swiss cantonal hospital. Specifically, the consumption of iodinated X-ray
contrast media (ICM) and cytostatics in the corresponding medical applications,
radiology and oncology, and their discharge into hospital wastewater and afterwards the
municipal wastewater treatment plant were analyzed. Emission levels within one day and
over several days were found to correlate with the pharmacokinetic excretion pattern and
the consumed amounts in the hospital during these days. ICM total emissions vary
substantially from day to day from 255 to 1'259 g/d, with a maximum on the day when
the highest radiology treatment occurred. Parent cytostatic compounds reach maximal

emissions of 8-10 mg/d. 1.1%, 1.4% and 3.7% of the total excreted amounts of the cytostatics 5-fluorouracil, gemcitabine and 2',2'-difluorodeoxyuridine (the main metabolite of gemcitabine), respectively, were found in the hospital wastewater, whereas 49% of the ICM sum was detected, showing a high variability among compounds. These recoveries can essentially be explained by the high amount administered to out-patients (70% for cytostatics, 50% for ICM), therefore only part of this dose is expected to be excreted on-site. In addition, this study points out critical issues to consider when sampling in hospital sewer systems. Flow proportional sampling over a longer period is crucial to compute robust hospital mass flows.

1 Introduction

Hospitals are sources for pharmaceuticals and disinfectants, and can be seen, besides households and industries, as hotspots for the discharge of these emerging contaminants into the sewer network. If not degraded in the municipal wastewater treatment plants (WWTP), they reach surface waters, with potential impact on the ecosystem and human health (1,2). Within the top 100 active compounds list of the Swiss national sales data of pharmaceuticals, 18 % of the medicaments' total volume is being administered in hospitals (3).

The occurrence of specific iodinated X-ray contrast media (ICM) (4,5), anti-tumor agents (6-8), carbamazepine, diclofenac and metamizole (9,10), as well as antibiotics (11,12) in hospital effluents have been reported. ICM (13) and cytostatics (14) are administered mainly in hospitals and therefore high amounts are expected in the hospital sewer. ICM are 100% dispensed in radiology applications and the consumption of the cytostatic cyclophosphamide in hospital amounts to 70% of its total consumption. The

occurrence and fate of cyclophosphamide and ifosfamide were studied in WWTPs and surface waters in Switzerland, and were found in concentrations from ≤ 50 to 170 pg/L in surface water (15). Due to a lack of studies on chronic effects on aquatic organisms, a final risk assessment cannot be made. Being intentionally designed to inhibit DNA synthesis, damage the DNA as well as being themselves carcinogenic and teratogenic, potential of cytostatics for causing adverse environmental effects is high, although still not proved (16). 5-fluorouracil was discovered as one of the most toxic and also highly used cytostatic compound by Zounkova et al. (17). ICM are not toxicologically relevant, but in general highly persistent polar compounds, measured in groundwater up to 2.4 $\mu\text{g/l}$ for iopamidol (18). Due to the high administration of ICM and cytostatics in hospitals, these institutions are presumed to be one of the major point sources for emission in hospital wastewater and contamination of the aquatic environment. In Switzerland as in the majority of other countries, hospital wastewater is not treated separately (except for radioactive compounds), and is released into the public sewer system together with domestic wastewater. As Pauwels and Verstraete (19) report, data are needed for the assessment of the potential impacts of hospital emissions of organic micropollutants and multiresistant microbial strains into the environment. The toxicity is considered to be 5-15 times higher in hospital wastewater than in domestic wastewater (20).

This study aimed to perform a time resolved mass flow analysis of hospital drugs – six ICM: iopamidol, iomeprol, iopromide, iohexol, ioxitalamic acid and amidotrizoic acid (diatrizoate); two cytostatics: 5-fluorouracil, gemcitabine and one human metabolite of gemcitabine, 2',2'-difluorodeoxyuridine (dFdU) – analyzing their consumption in a representative hospital and their occurrence in the hospital wastewater.

The chosen Cantonal Hospital belongs with 415 occupied beds to the 10 biggest Swiss hospitals. Volume-proportional sampling is done to be able to compare measured emissions with the actual consumption levels to come up with amounts of the analyzed drugs really excreted into the hospital sewer system, what has not been reported so far. These results enable more refined modeling of real mass flows from hospitals and comparison to mass flows from domestic wastewater, what was reported for carbamazepine, diclofenac and metamizole (9,10). Such evaluations allow for predicting pollutant loads in surface waters, and for assessing the significance of hospital discharges on the surface waters quality.

2 Material and methods

2.1 Description of sites and sampling

2.1.1 Cantonal Hospital and sampling of its wastewater

The cantonal hospital has 415 occupied beds and produces a volume of 135'000 m³/year or 1 m³/(bed·day) wastewater. It contains 1% out of a total of 41215 occupied stationary beds within Switzerland. This number is based on statistics of major hospitals in 2004 (21) and additional calculation of beds for smaller hospitals based on the official hospital typology of the Swiss Federal Office for Statistics. The sampling location included all medical departments of interest, in particular radiology and oncology institutes, and excluded laboratory chemical water, kitchen and laundry wastewater. In case of rain events, storm water was discharged from roofs and from half of the hospital parking area (0.13 ha). Therefore, dry weather conditions were chosen for the sampling period in order to avoid sample dilution. The campaign was divided in three successive phases as illustrated in S2, Fig.S1 and Tab.S1 (Supporting Information): a one-week test

phase (flow measurements), a 12-days sampling phase (18h- composite day-samples from 5:00-23:00 and 6h-composite night-samples from 23:00-5:00) and a one-day sampling phase (3h-composite sample over 24 hours).

The hospital wastewater flow rate profile was measured continuously during the test phase, using a flow meter (American Sigma 950) triggering the auto-sampler (American Sigma 900max). During the sampling period the average flow was 15.8 m³/h (min 4.0 m³/h; max 205.7 m³/h). Since concentration variations are a priori unknown and expected to be high, samples must be collected with a flow- or volume-proportional mode to obtain representative composite samples. Due to the sewer depth of eight meters, at least 90 seconds of dead time are required between samples for back flushing the tube. To achieve sufficient accuracy for the volume of an individual sample, a minimum of 75 ml must be pumped each time. The flow in the sewer during the nights of the test phase was substantially higher than the flow during the day. This was caused by back flushing the hospital's reverse osmosis installations. Given the limited storage capacity (24 L) the following volume-proportional day sampling scheme was applied: 75 ml were pumped each time after 2 m³ of wastewater had passed the sampling station. This resulted in an average sampling interval of eight minutes. Day and night samples were separated for the following reason: Cytostatics concentrations were presumed to be non-detectable in diluted night or even mixed samples. For the constitution of the mass flow profile over one day, eighteen 1h- to 1.5h- composite samples were taken, filtered (S2, Supporting Information) and mixed flow proportionally to obtain nine 2h- to 3h- composite samples. 24h- composite samples for ICM analyses were obtained by flow proportional mixing of the 18h-day and 6h-night samples.

As hospital wastewater is highly contaminated and for certain pharmaceuticals and pathogens up to about 100 times more polluted than municipal WWTP influents, considerations of full personal and instrumental safety measures are recommended for the work with hospital effluents (22). All instruments in contact with raw hospital wastewater were autoclaved or chemically disinfected when thermal sterilization was not applicable. More details are given in the Supporting Information (S1).

2.1.2 Assessment of sampling uncertainty

To determine the expected sampling uncertainty (23), the following data are needed (Tab.S2, Supporting Information): information about the sewer network (e.g. location of buffer tanks), distance from sanitary appliances to the sampling point, target medical departmental activities and number of toilet flushes, the administered dose and the number of toilet flushes related to the target active compounds.

For the average sampling interval of eight minutes the uncertainty was calculated assuming different numbers of toilet flushes per 18-hour period. In the case of only one or two toilet flushes, representing one patient being treated in the hospital but excreting a part also at home, a sampling uncertainty of -100 to +130% (68%-quantile) was estimated. For 18 toilet flushes (stemming from about 2-5 patients per day with 4.5 toilet flushes per patient) the sampling uncertainty is approximately $\pm 50\%$, for 30 pulses (6-9 patients per day) the deviation is around $\pm 40\%$, and for 50 pulses (10-12 patients per day) the deviation is in the order of $\pm 30\%$ (see also Tab.S8, Supporting Information).

2.1.3 Description of WWTP and sampling of its wastewater

The hospital wastewater is discharged to a WWTP which treats the wastewater of 115'000 inhabitants. The influent flow rate reaches 49'000 m³/d at dry weather, what is

by a factor of 150 higher than the flow rate of the hospital. The hydraulic retention time in the WWTP amounts to 16 h, while the travel time of the wastewater from the hospital to the WWTP is only 1 h. On two successive Mondays, two 24h- composite flow proportional wastewater samples were taken after the primary clarifier (WWTP influent) and after sand filtration (WWTP effluent), both starting at 7:00 am.

2.2 Analytical methods

2.2.1 Samples preparation and measurement

The analytical methods were adapted from Ternes et al. (24) for ICM and from Kovalova et al. (25) for cytostatics. More details on analytes, sample preparation and measurement are given in the Supporting Information (S3).

2.2.2 Quality assurance

Concentrations were calculated by using external calibration with standards in nanopure water and relating to the peak area of the internal standard. For ICM, a comparison with standard addition was done and the deviation to external calibration was for hospital wastewater 7(±9)%. The absolute extraction recovery of the internal standard DMI was 75-135%. Absolute recoveries (67-138% for ICM, 40-79% for cytostatics) and relative recoveries (65-129% for ICM, 54-118% for cytostatics) were calculated for each compound and wastewater matrix over the whole method (Tab.S5, Supporting Information). Results were not corrected by the relative recoveries, except for dFdU. Limits of quantification (LOQ) for ICM range from 0.2-20 µg/l for hospital wastewater and from 0.01-0.3 µg/l for WWTP wastewater; LOQ for the cytostatics range between 0.9 - 9 ng/L for hospital wastewater.

2.3 Pharmacokinetic information on the analytes

ICM have an average half-life time in the human body of around 2 h, 75% of the administered dose is excreted within 4h and nearly 100% within 24 hours (more details are given in Tab. 2). Ioxitalamic acid and iopamidol follow different absorption ways. Ioxitalamic acid is consumed via the oral way (Telebrix Gastro™) and excreted via the intestine. In a second specific application, Telebrix™ is filled in the bladder and excreted in lavatories directly after diagnostic because of bladder pressure. In arthrography applications, iopamidol is injected in articulations and excreted through blood into urine.

5-fluorouracil is eliminated in the human body by the liver and other tissues and together with metabolites urinary excreted. When administered by intravenous bolus, elimination half life in plasma varies from 5 to 20 minutes. 60-90% of the administered dose is excreted in urine within 24 hours (6 hours for unchanged 5-fluorouracil), primarily as α -fluoro- β -alanine (approx. 80%) but also as α -fluoro- β -ureidopropionic acid and as unchanged 5-fluorouracil (each approx. 10% of the excreted dose (26)). However, the excretion of 5-fluorouracil can vary from patient to patient and ranges between 2-89% (27,28). Taking into account the very short half-life of 5-fluorouracil, it can be expected that part of the excretion takes place at the hospital also in case of out-patient treatment. The urinary excretion rate of 5-fluorouracil after administration of capecitabine, the oral form of 5-fluorouracil, is only 0.54% (29). The elimination of gemcitabine is rapid with a half live of approximately 8 minutes. The gemcitabine metabolite dFdU has a long terminal phase if biphasic elimination kinetics with half lives between 2.5 and more then 24 hours (30). In average 5% of the total drug is recovered as gemcitabine in urine and all

appears during the first 6 hours after treatment. 60% of the administered gemcitabine is urinary excreted as the metabolite dFdU within 24 hours.

3 Results and discussion

3.1 Relevance and consumption of investigated ICM and cytostatics

The consumption dynamics of target compounds are highly complex and variable. In 2004, a total of 19.6 tons of the six ICM was used in Switzerland (3). The daily consumed amount of each ICM range from 4.5 - 19 kg/day (Tab.S6, Supporting Information). Iopromide and iohexol are used in the highest amounts. The consumed amounts of diatrizoate are not known. These numbers can be compared to the annual stock variations of the hospital central pharmacy (transfer to the individual department stock). In the Cantonal Hospital 523 g/day of the five ICM were used in 2005, what corresponds to 1% of the Swiss national consumption in 2004 (53.6 kg/day). This number correlates nicely with the relative amount of occupied stationary beds of the hospital (415 out of 41'215 beds). In 2005, iopamidol and iopromide are used in the highest amounts in the hospital, while in 2006 iomeprol and iopamidol show the highest consumption, demonstrating the high variability from year to year, following the economic market.

For the cytostatics, only the amounts consumed in the cantonal hospital in 2006 are available (Tab.S7, Supporting Information). In total, 7.8 kg cytostatics were consumed with 40 different active ingredients, with 5-fluorouracil and gemcitabine in the highest quantities. Since the excretion of cytostatics is highly variable from compound to compound, the relative importance of the compounds can be better judged on the basis of expected excreted amounts. 5-Fluorouracil is expected in the highest amounts in the hospital wastewater (187 g/year), followed by methotrexate, cyclophosphamide, carboplatin and gemcitabine.

3.2 Monitored drugs and correlation with pharmacokinetic data

Concentrations of ICM measured in hospital wastewater were in the high $\mu\text{g/l}$ level ($<5\text{'2'400 } \mu\text{g/l}$), for the cytostatics in the low ng/l level ($<0.9\text{'38 ng/l}$ for parent compounds). The ranges of concentrations of the ICM target compounds are: iomeprol ($28\text{'2'400 } \mu\text{g/l}$), iohexol ($<20\text{'1'700 } \mu\text{g/l}$), iopromide ($<5\text{'1'390 } \mu\text{g/l}$), iopamidol ($<10\text{'1'120 } \mu\text{g/l}$), ioxitalamic acid ($15\text{'550 } \mu\text{g/l}$). Diatrizoate was not consumed at the hospital and not detected ($<0.2 } \mu\text{g/l}$). The measured cytostatics concentrations lie between $<5\text{'27 ng/l}$ (5-fluorouracil), $<0.9\text{'38 ng/l}$ (gemcitabine) and $<9\text{'839 ng/l}$ for dFdU, the human metabolite of gemcitabine.

Also in the WWTP, ICM concentrations vary substantially: between $0.02 } \mu\text{g/l}$ (iopromide) and $19 } \mu\text{g/l}$ (iohexol) in the WWTP influent. The concentration of iohexol in the influent reached $19 } \mu\text{g/l}$ on Monday 30.04.2007 but only $0.69 } \mu\text{g/l}$ the next Monday. Concentrations in the WWTP effluent were between $0.4 } \mu\text{g/l}$ (iohexol) and $5 } \mu\text{g/l}$ (iopamidol). The focus of this study was on hospital wastewater and not on WWTP, so only two samples were taken in the WWTP to show exemplary their occurrence and high variation in concentration. To calculate elimination rates in the WWTP, the hydraulic retention time (16 h) would have to be considered for sampling and more samples are needed to do mass flow calculations. It is known from literature that elimination of ICM in conventional wastewater treatment is small (18,31-34). Only iopromide is degraded by 60-70%. As expected, none of the analyzed cytostatics were detected in the 24h-composite samples of the WWTP influent or effluent. Since concentrations in hospital wastewater are lying in the low ng/l range, further dilution by factor 100 results in concentrations below LOQ.

The mass flow profiles of ICM over one day show high variations of instantaneous individual loads from 0.9 to 829 g/d (Fig. 1), with maximal emissions between 12:00 and 17:00 (1'100-1'200 g/d of ICM sum). These results were well expected when looking at the pharmacokinetic properties which suggest that 50% of the ICM are excreted within 2 hours after application (see section 2.3). An application in the morning or afternoon is therefore inducing the measured emissions.

Like ICM, mass flow profiles of cytostatics show high daily variations (Fig. 1). Well detectable levels of all three compounds were measured between 11:00-20:30. In the night fractions, no parent cytostatic compound was detected above LOQ, while the human metabolite dFdU was observed also during the night. The measured mass flow profile is in agreement with the pharmacokinetic knowledge. The oncology treatments are done during the day, and the major part of the parent compounds were expected to be emitted also during the day, after 1 h for 5-fluorouracil and within 6 h for gemcitabine. The profile of gemcitabine presents the excretion pattern of one hospitalized patient – the only patient treated with this substance (2'300 mg) that day – staying overnight. Assuming a morning treatment, he excretes the gemcitabine and its metabolite dFdU in a first (09:35-11:45) and second period (14:25-17:05), which is physiologically relevant. The metabolite is excreted in higher amounts: ratios of dFdU / gemcitabine are 10 resp. 3 in the two periods, which are comparable to the expected ratio of 6-17 in the excreted urine within the first six hours after infusion (30). In the night samples, longer elimination half lives for the metabolite dFdU explain the presence of the metabolized form.

3.3 Correlation between consumption data and emissions in hospital wastewater

The exact consumption amounts and number of treated patients during the sampling phase were made available by the radiology and oncology departments (Tab.1). On average, 24 patients per day are treated in radiology and 3-4 patients in oncology with the investigated drugs. During the sampling period, 1149 g/day of the target ICM were dispensed to radiology patients, while only 4 g/day of cytostatics have been consumed. Compared to the average consumption in the hospital in 2006 (see section 3.1), about the same amount of ICM, but 4.5 times less cytostatics are used.

Measured emissions and the comparison to their consumption in medical departments during the sampling period are shown in Fig. 2, Tab. 2 and Fig. S2. Calculations were done for hospitalized patients and out-patients.

Over the week, mass load profiles show high variations for individual ICM as well as for the sum of all ICM (255-1'259 g/d). For the ICM consumed in the highest amounts– iomeprol, iohexol and ioxitalamic acid – a good correlation exists between consumption data and measured loads. 15-71% was recovered in the sewer. Individual ICM and their sum reached maximal levels on Friday, when the radiology department operated at its highest capacity. During week-ends, only the emergency computer tomography application was in operation, where iomeprol and ioxitalamic acid were used, which were also found in the wastewater in significant amounts. Occurrence of iopromide and iopamidol on days when no consumption occurred cannot be explained, except if an improper disposal occurred, if consumption data are wrong or if patients who consumed ICM in private radiology institutes came to the hospital for further treatment. Over the sampling period, 49% of the consumed and excreted sum of all ICM was

recovered. For 6 or more patients per day excreting an ICM into the sewer, what is the case for the highly used iomeprol, iohexol and ioxitalamic acid, a sampling uncertainty of 30-40% was calculated (see section 2.1.2). This needs to be considered when interpreting this result. However, deviations between consumed and measured amounts can be mainly explained by the fraction of out-patient diagnostics in radiology. According to the Head of the Radiology Department, on average about 50 % of the doses are administered to out-patients, what corresponds nicely to the recovered total amount.

Concerning the cytostatic 5-fluorouracil, the highest loads of 7.5 mg/d (Wednesday) corresponds also to the highest daily consumption (Fig. 2). The mass flow profile of 5-fluorouracil over the whole week correlates linearly with the intravenous consumption pattern ($R^2 = 0.975$, last point rejected, Fig.S3, Supporting Information). The consumption of capecitabine – the oral form of 5-fluorouracil, only administered to out-patients – is not detected in the hospital sewer, as it was probably excreted entirely in patients' households. Moreover, the urinary excretion rate of 5-fluorouracil after administration of capecitabine is about 20 times smaller than for the intravenous application. During the last sampling day no 5-fluorouracil was detected, even though there should have been an input. However, this input is predicted from the treatment of one single hospitalized patient (Tab.1), who might not have excreted into the toilet of the hospital for personal reasons. For gemcitabine and its metabolite, a weaker correlation exists between measured loads and the consumption (Fig.2). Measureable concentrations were found when a treatment took place, and whenever gemcitabine is present, also dFdU was found. The highest load of 9.7 mg/d for gemcitabine (last sampling day) was found when also a relatively high daily consumption occurred. Such high variations of mass

loads of cytostatics in hospital wastewater were also observed in an Austrian study (7) and are caused by the low number of patients receiving chemotherapy.

In average over the 9 days sampling period, the amount of 5-fluorouracil detected corresponds to 1.1% of the excreted quantity; for gemcitabine 1.4% of excretion, and for its metabolite dFdU 3.7% of excretion (Tab.2). For the interpretation of these results one first has to consider that the excretion rate can vary from patient to patient (section 2.3). A comparison can be done to the study performed by Mahnik et al. (7) at Vienna University Hospital. They sampled wastewater directly from the oncology in-patient ward fed exclusively by 3 toilets and 3 showers (used by 18 patients). The concentrations of 5-fluorouracil were as high as 124 µg/L and loads recovered were in line with calculated loads when considering an excretion rate of 2%. When using a 2% excretion rate (instead of the average rate of 10% used for our calculation, Tab. 2), 5.5% of the expected excreted amount of 5-fluorouracil is recovered in the hospital sewer.

The main reason for the relatively low recoveries lay in the fact that the oncology department provides a high amount of ambulatory treatments: for 5-fluorouracil, 63% were out-patients and 67% of the total quantity is administered to out-patients; for gemcitabine, the percentages are slightly higher (80% resp. 76%). Therefore, only about 30% of the administered dose is estimated to be excreted on-site into the hospital sewer. Another reason for the low recovered loads lays in the relatively high sampling uncertainty especially for cytostatics which occurred due to the sampling procedure (see section 2.1.2). Because only a few patients are contributing to the daily load, the chance that toilet pulses were missed is high and an uncertainty of up to 120-130% was calculated. This high sampling uncertainty is causing the large overall uncertainties

depicted in Fig.2 and in Tab.2 (details on uncertainty calculation in S4, Supporting Information). Moreover, there are indications that cytostatics are degraded already in the sewer system (35).

Addressing an issue that became relevant in the last years, this study pilots mass flow considerations for two groups of relevant xenobiotics and contributes to the current knowledge base. It shows that hospitals are indeed a point source for ICM. 49% of the administered amount was recovered in the hospital sewer, the rest is most probably excreted into domestic wastewater carried home by the 50% of out-patients treated at the hospital. Cytostatics are also found in relatively high amounts in the hospital sewer, however, only between 1.1 and 5.5% are recovered in the sewer and about 70% is carried home by out-patients. Therefore, the total volume of drugs ending up in the hospital sewer is smaller than the administered volume, accounting to 18% of the medicaments' total volume, and will further decrease when out-patient treatment is increasing as predicted for the future. Moreover, insight in the complexity of describing the hospital consumption and the excretion dynamics are given. An adequate sampling procedure was found to be crucial for mass flow analysis due to high input fluctuations. When continuous, flow-proportional sampling is not possible (e.g. as done in other studies (7,9)), a method is described on how to calculate optimal sampling intervals (fractions every 0.5-1 minute in our case) and sampling uncertainties. Sampling periods over several weeks are preferable. The obtained results on mass flows can be used as basis for models to predict concentrations of analytes in the surface water system.

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Supporting Information Available

Biosafety; hospital wastewater flow profile; input data for sampling optimization modeling; analytical methods and analytical parameters; annual consumption data; mass flow profiles of ICM and cytostatics over 8-9 days; linear correlation between the intravenous consumption of 5-fluorouracil and its emission in hospital wastewater; calculated overall measurement uncertainty. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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Figure 1. Mass flow profile of ICM (*top*) and cytostatics (*bottom*) in hospital wastewater over one day (Monday 07.05.2007). The continuous dark line represents the sum of the six ICM mass flows. Points are the calculated values based on the measured concentrations within the composite sampling time interval. The horizontal dotted line corresponds to the daily average of the six ICM. Minimum and maximum of extraction duplicates are described with the error bars.

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Figure 2. Mass flow profiles of ICM and cytostatics in hospital wastewater over 8 resp. 9 days (*black lines*) compared to total predicted excreted amounts (*bars*) during the sampling period. Error bars of measurements incorporate sampling uncertainty, the analytical error from duplicate measurements and the uncertainty due to the water flow measurements (details in S4, Supporting Information).

501 **Table 1.** Exact consumption data from the radiology clinic (ICM, intravenous i.v., in articulation or oral) and the oncology clinic
502 (cytostatics, i.v. or oral capecitabine tablets), over the sampling period. The number of treated patients is available in parenthesis: exact
503 numbers for oncology; deduced number from dose per patient in radiology. Ioxitalamic acid is consumed via the oral way or filled in the
504 bladder*. 5-fluorouracil consumption data do not include the out-patient treatment by pump infusion for 22 hours to 7 days.

Daily consumption of active substances

ICM (in g/d)	Iopromide (i.v.)	Iopamidol (articulation)	Iomeprol (i.v.)	IoHexol (i.v.)	Ioxitalamic acid (oral)	Diatrizoate
Mon. 30.04.2007	0	37 (4 pat.)	343 (6 pat.)	1'126 (17 pat.)	66 (3 pat.)	0
Tue. 01.05.2007	0	0	367 (6 pat.)	0	33 (2 pat.)	0
Wed. 02.05.2007	156 (3 pat.)	25 (3 pat.)	555 (10 pat.)	725 (11 pat.)	165 (8 pat.)	0
Thu. 03.05.2007	0	6 (1 pat.)	278 (5 pat.)	654 (10 pat.)	264 (13 pat.)	0
Fri. 04.05.2007	137 (2 pat.)	12 (1 pat.)	653 (11 pat.)	909 (14 pat.)	363 (18 pat.)	0
Sat. 05.05.2007	0	0	457 (8 pat.)	0	66 (3 pat.)	0
Sun. 06.05.2007	0	0	221 (4 pat.)	0	33 (2 pat.)	0
Mon. 07.05.2007	0	0	392 (7 pat.)	802 (12 pat.)	198 (10 pat.) + 150 (1 pat.)*	0
Total on 8 days (g)	293 (5 pat.)	80 (9 pat.)	3'266 (57 pat.)	4'216 (64 pat.)	1'338 (60 pat.)	0
ICM total consumption on 8 days = 9'193 g (195 pat.)						

Cytostatics (in mg/d)	5-fluorouracil			Gemcitabine	
	Ambulant patients (i.v.)	Hospitalized patients (i.v.)	Ambulant patients (tabl.)	Ambulant patients (i.v.)	Hospitalized patients (i.v.)
Mon. 30.04.2007	2'500 (3 pat.)	0	0	5'800 (3 pat.)	2'300 (1 pat.)
Tue. 01.05.2007	0	0	0	0	0
Wed. 02.05.2007	3'600 (5 pat.)	43 (1 pat.)	2'600 (1 pat.)	3'800 (2 pat.)	0
Thu. 03.05.2007	1'300 (2 pat.)	43 (1 pat.)	0	0	0
Fri. 04.05.2007	0	43 (1 pat.)	2'500 (1 pat.)	1'800 (1 pat.)	0
Sat. 05.05.2007	0	43 (1 pat.)	0	0	0
Sun. 06.05.2007	0	43 (1 pat.)	0	0	0
Mon. 07.05.2007	950 (2 pat.)	43 (1 pat.)	0	0	2'300 (1 pat.)
Tue. 08.05.2007	0	3'793 (1 pat.)	0	3'300 (2 pat.)	0
Total on 9 days (mg)	8'350 (12 pat.)	4'051 (7 pat.)	5'100 (2 pat.)	14'700 (8 pat.)	4'600 (2 pat.)
Cytostatics total consumption on 9 days = 36.8 g (31 pat.)					

Table 2. Calculated average emission of drugs in cantonal hospital during sampling period and comparison with measured emission. For 5-fluorouracil, only i.v. application was considered. The consumption of dFdU was set equal to the consumed amount of gemcitabine considering the weight difference*. Predicted loads were calculated based on the consumption and excretion, not including the amount of out-patients. Overall uncertainties were calculated for each day and minimum-maximum are given. Average, minimum and maximum recoveries were calculated based on the measured load relative to the predicted load for each day. For the sum of all ICM, the overall recovery over the whole period was calculated.

Compound	Average consumption during sampling period [g/day]	Half-life elimination from human body ($t_{1/2}$)	Excreted amount	Duration of full excretion	Predicted load [g/day]	Measured average load (min-max) [g/day]	Overall uncertainty of measured load	Average Recovery in hospital sewer (min-max) [%]
iopromide	37	2 h	>92 %	24-48 h	34-37	44 (0-343)	20-92%	2 (0-4.3)
iopamidol	10	2 h	>90 %	24-96 h	9-10	107 (0.6-384)	20-112%	1202 (8-3141)
iomeprol	408	2 h	100 %	24 h	408	279 (85-580)	54-73%	71 (28-147)
iohexol	527	2-3 h	100 %	24 h	527	89 (1.4-216)	20-54%	15 (4-24)
ioxitalamic acid	167	1-2 h	>95 %	24 h	159-167	47 (18-79)	36-102%	49 (17-118)
<i>sum of all ICM</i>	<i>1149</i>	<i>2 h</i>	<i>90-100 %</i>	<i>24 h</i>	<i>1134-1149</i>	<i>566 (255-1259)</i>	<i>28-63%</i>	<i>49</i>
5-fluorouracil	1.38	5-20 min.	10 % (2-89 %)	6 h	0.14 (0.03-1.23)	0.0021 (0-0.008)	74-112%	1.1 (0-3)
gemcitabine	2.14	8 min	5 % (1-10 %)	6 h	0.11 (0.02-0.21)	0.0013 (0-0.01)	86-123%	1.4 (0.1-6)
dFdU	2.15*	2.5 - 24 h	60 % (29-86 %)	24 h	1.29 (0.62-1.85)	0.058 (0.007-0.215)	20-123%	3.7 (0.7-11)

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518	Table of Content Brief:
519	X-ray contrast media and cytostatics are analyzed in a Swiss hospital and the measurements are compared to actual consumed amounts
520	during the sampling period.
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