REVIEW ARTICLE

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The Safety Profile of Sustained Release Paracetamol During Therapeutic Use and Following Overdose

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Contents

Abstract

Sustained release (SR) formulations of paracetamol (acetaminophen) have been introduced in several countries to provide lasting pain relief and reduced risk of rebound pain. However, few studies have evaluated the safety of paracetamol SR formulations.

To assess the available published safety data regarding SR formulations of paracetamol, the EMBASE and MEDLINE databases were searched from 1980 to June 2003 for published worldwide human experience with paracetamol SR formulations. All publications that included any information about ingestion of any paracetamol SR formulation were systematically reviewed and abstracted by trained staff. The literature searches returned a total of 14 references containing safety data on paracetamol SR. In addition, the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers (AAPCC) database was searched for human exposure cases. The TESS database yielded 3003 cases from 1994 to 2002 that involved a paracetamol SR product.

The available information indicates that the adverse event and safety profile of paracetamol SR is very similar to immediate release (IR) formulations of paracetamol. During therapeutic use, minor effects such as gastrointestinal upset and headache may occur. The rate of these effects varies substantially among

studies but overall does not appear to be different between the SR and IR formulations of paracetamol. Overdose with paracetamol SR is expected to cause liver injury similar to overdose with IR formulations. The number of human exposure cases has increased since introduction of the SR formulation; however, sales of the SR formulation amounted to 7.5% of all paracetamol sales but accounted for 2.5% of the cases reported to poison centres. There were two deaths recorded in the TESS database: both were the result of multiple drug ingestion. No cases of death or unusual types of toxicity have been described from an overdose of paracetamol SR alone.

After approximately 40 years of use as an immediate release (IR) formulation, a sustained release (SR) formulation of paracetamol (acetaminophen) was introduced in 1994 in the US. Other SR formulations have since been introduced in other countries. In 2002, poison centres in the US recorded 700 contacts regarding exposure to paracetamol SR.[1] The paracetamol SR product available in the US is a bi-layered, extended-release tablet that contains 650mg of paracetamol. One side of the tablet contains paracetamol IR 325mg, while the other side contains 325mg of paracetamol in a matrix formulation that releases the drug at a slower rate.[2] The dosage of paracetamol SR recommended by the manufacturer in the US is 1.3g every 8 hours as opposed to the recommended dosage of the extra strength formulation of 1g every 4 hours, not to exceed 4g per day.[2] The proposed benefit of the SR product is longer lasting pain relief and reduced risk of rebound pain. In the US, it has been approved for use in adults and children ≥12 years of age.

According to ACNielsen data,[3] the proportion of paracetamol tablet sales in the US comprised by the SR formulation has increased from 1.1% in 1994 to 7.6% in 2002. It is evident from rising sales that the SR formulation of paracetamol is becoming a more popular choice of over-the-counter analgesic. Despite the increasing popularity of this formulation, few studies have evaluated the safety of paracetamol SR formulations. This review systematically summarises the safety data available regarding SR formulations of paracetamol.

1. Methods

1.1 Medical Literature

The MEDLINE and EMBASE databases were searched from 1980 to June 2003 for literature that was published on worldwide human experience with paracetamol SR formulations. The keywords used were: '103-90-2'(the chemistry abstract service number), 'paracetamol', 'acetaminophen' OR 'APAP' AND 'extended release', 'extended relief', 'sustained release', 'sustained relief' OR 'slow release'. The reference lists of articles returned were also hand searched for other related articles. Foreign language articles were translated and included. In addition, publications that cited the previously identified literature were searched using the Web of Science. Further citations were also solicited from two manufacturers of paracetamol SR products.

All publications that met the search criteria and included information about ingestion of any paracetamol SR formulation were systematically reviewed and abstracted by trained staff. Standardised data collection templates for each group were created in order to systematically abstract the data from each publication. If the same patients were included in more than one publication, only the most recent and complete publication was included. Duplicate publications and letters/reviews were excluded. All generic references to paracetamol SR that did not include the specific product formulation were assumed to be the combination product containing both paracetamol SR and IR.

1.2 Poison Centre Database

In addition, the Toxic Exposure Surveillance System (TESS) of the American Association of

Poison Control Centers (AAPCC) database was searched for human exposure cases from 1994 to 2002. The search was conducted using five standard paracetamol SR product identification numbers established by the AAPCC for coding purposes. The AAPCC is a nationwide organisation of poison centres that collects and analyses national poisoning data. The AAPCC TESS database contains standardised data fields that are used by all poison centres in the US. The proportion of the US covered for the years involved in this report varied from 83% in 1994 to 100% for the year 2002. In most cases that have the potential for injury, a follow-up call is performed to assist in management of the patient. After a case is followed until outcome can be determined, it is closed and uploaded to the AAPCC main database. The TESS data set resulting from the specified search was analysed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA) and EpiInfo 2002 (Center for Disease Control, Atlanta, GA, USA) statistical software. Descriptive statistics as well as chi-squared analysis were conducted.

2. Results

2.1 Medical Literature

2.1.1 Therapeutic Dose

A total of 21 references containing safety data on paracetamol SR were identified. Four publications were excluded because of duplicate publication and three were letters/reviews that did not provide patient data. Of the 14 remaining references, two investigated the pharmacokinetics of paracetamol formulations, seven prospectively investigated the efficacy and/or safety of a therapeutic dose (table I), and five involved an overdose ingestion.

Overall, results from six prospective studies (five in adults, one in children) indicate that the tolerability of paracetamol SR formulations at therapeutic doses is comparable to that of paracetamol IR. In an 8-hour, randomised double-blind trial, febrile children (aged 2–11 years) were given two doses of either paracetamol SR as a granular substance sprinkled on apple sauce or a paracetamol IR elixir 4 hours apart (dose not reported for either formulation). A total of ten adverse events were reported in eight (6.8%) of the 118 patients in the safety cohort (four in each treatment group).[4] Two patients in the SR group and four in the IR group withdrew from the trial because of an adverse event. None of these events was serious or potentially serious in nature. Two patients had adverse events that were judged by the investigator to be related to study medication. Both involved an episode of vomiting: one event occurred in each group. No differences in adverse event reports were found between paracetamol SR and IR groups. All adverse events were reported irrespective of whether or not they were considered related to study medication.

Two separate studies used painful laser stimulation in a total of 25 healthy volunteers to compare paracetamol IR and SR.[5,6] Between the two studies, one patient reported two adverse events: headache and nausea during treatment with paracetamol SR.[5]

Bacon et al.[7] compared the efficacy and safety of a dosage of two paracetamol SR 665mg tablets taken three times daily with the outcome of patients receiving a dosage of two paracetamol IR 500mg tablets taken four times daily in 403 patients with osteoarthritis. The distribution of adverse effects between the paracetamol SR and IR groups during the 7-day treatment phase was similar by body system, severity and relationship to the study drug. One serious adverse event, mild left hemiparesis, occurred during the run-in period and was judged to be unrelated to the study medication. Another patient with a history of food allergy and aspirin (acetylsalicylic acid) sensitivity was withdrawn from the study following a severe allergic reaction to the investigational SR formulation. AST and γ-glutamyl transferase levels were normal in this patient at enrolment, increased 5- to 10-fold when tested 3 days after withdrawal and then returned to normal. These increases were attributed to the patient's allergic reaction. Overall, adverse events were responsible for the withdrawal of 20 patients (ten patients in each group) from the study. The most common events were headache, diarrhoea, depression, influenza, nausea, rash and vomiting.

A published abstract of 106 patients compared paracetamol SR with naproxen in the treatment of osteoarthritis. The rate of gastrointestinal adverse effects was lower with paracetamol SR 3900 mg/day tablets than with naproxen 1000 mg/day (23.1% and 29.6%, respectively).[8] The severity of effects was

Table I. Summary of safety data from clinical trial articles involving administration of a therapeutic dose of sustained release (SR) paracetamol (acetaminophen)[a]

Study	No. of subjects	Indication	Dose	No. of AEs (%) and patients reporting AEs	Reported AEs
Wilson et al.[4]	118[b,c]	Febrile children	Two doses of IR given 4h apart or one dose of SR (specific dose not provided)	Ten AEs: four (7%) patients in SR group, four (7%) patients in IR group	Vomiting, disorientation, confusion, extreme irritability
Nielsen et al.[5]	15	Laser-induced pain	5d of IR 1g every 6h, 5d of SR 2g every 12h and 5d of placebo taken every 6h (crossover)	One (7%) patient experienced two AEs during SR treatment	Headache and nausea (one patient) during first 3d of SR paracetamol administration
Nielsen et al.[6]	10	Laser-induced pain	One dose each of IR 0.5g, IR 1g, SR 2g and placebo (crossover)	None reported	NA
Bacon et al.[7]	403	Osteoarthritis	7d of either four doses of IR 1g or three doses of SR 1.33g	24 AEs: 13 (54%) in SR group, 11 (46%) in IR group	Run-in period: mild left hemiparesis Study period: severe allergic reaction (SR = one patient), headache (SR = two IR = five), diarrhoea (SR = two, IR = two), influenza (IR = two), depression (SR = two), nausea (SR = two, IR = two), rash (SR = two, IR = none), vomiting (SR = two)
Lee et al.[8]	106	Osteoarthritis	SR 3.9 g/d or naproxen 1 g/d for 8wk	Not reported	Gastrointestinal AEs such as epigastric pain and dyspepsia (30% in naproxen group, 23% in paracetamol SR group), abnormal transaminase level elevation (one in naproxen group, two in paracetamol SR group)
Coulthard et al.[9]	627	Oral surgery	One dose of IR 1g or one dose of SR 1.33g	604 AEs: 166 (53%) patients in SR group, 163 (52%) patients in IR group	Nausea, vomiting, dystonia, hypesthesia, paresthesia, dizziness, face oedema, headache, infection, haemorrhage
Strom et al.[10]	274	Oral surgery	Two doses of either IR 0.5g, IR 1g, SR 1g, SR 2g, IR 0.5g + SR 1.5g or IR 0.25g + SR 0.75g during a 12h study period	25 patients reported AEs: ten (15%) in SR only groups, seven (10%) in SR + IR groups, eight (12%) in IR only groups	Most common AEs overall were nausea and tiredness

a The primary purpose of each study was the assessment of efficacy and/or safety.

b Product tested was a test product, not available to consumers at the time of the study.

c In total, 118 patients received at least one dose of study medication and were included in the safety cohort; however, six patients (two paracetamol SR, four paracetamol IR) withdrew from the trial before completion.

AE = adverse event; **IR** = immediate release paracetamol; **NA** = not applicable.

not specified and no additional safety data were provided.

Coulthard et al.[9] compared a single dose of paracetamol SR 1330mg with paracetamol IR 1000mg for pain relief following oral surgery. Adverse events were reported by 166 (52.9%) patients in the SR group compared with 163 (52.1%) patients in the IR group. Most events were unrelated to study medication. The most frequent events were nausea, vomiting, dystonia, hypesthesia, paraesthesia, dizziness, face oedema and headache. Three serious adverse events occurred in three different patients (postoperative haemorrhage, hypotension and acute postoperative wound infection), all of which were judged to be unrelated to the study medication.

Strom et al.[10] evaluated a total of 274 oral surgery patients randomly assigned to a single dose of medication in one of six treatment groups: (i) high-dose SR (2000 mg); (ii) low-dose SR (1000 mg); (iii) high-dose IR/SR (IR 500mg + SR 1500 mg); (iv) low-dose IR/SR (IR 250mg + SR 750 mg); (v) high-dose IR (1000 mg); and (vi) low-dose IR (500 mg). Adverse events were noted by four patients in the high-dose SR group, six patients in the low-dose SR group, four patients in the high-dose IR/SR group, three patients in the low-dose IR/SR group, two in the high -dose IR group and six in the low-dose IR group. The events were similar between treatment groups. The most common complaints were nausea (ten patients) and tiredness (eight patients). The severity of these effects was not indicated.

2.1.2 Overdose

Two randomised crossover trials enrolling a combined total of 24 patients compared the pharmacokinetics of paracetamol SR with the pharmacokinetics of paracetamol IR following a simulated overdose (single dose of 75 mg/kg; normal therapeutic dose 15 mg/kg).[11,12] The same dose and formulation of paracetamol (Tylenol® [1] Extended Relief) was used in both studies. Despite the large dose, the SR formulation was well tolerated. One study reported an unspecified number of complaints of nausea and headache,[11] while the other study reported three subjects (21%) with nausea and one subject (7%) with lightheadedness.[12]

Five retrospective reports of overdose with paracetamol SR in 17 patients were found.[13-17] Overall, there was only one male patient and the patient age range was 13–43 years. With one exception, these cases occurred in the US and were generally managed medically in the same manner as for overdose with the IR formulation of paracetamol.

One potential difference in the management of patients receiving SR and IR formulations involves the use of the Rumack-Matthew nomogram in assessing the need for acetylcysteine treatment. In the US, treatment with acetylcysteine is typically initiated if the serum paracetamol concentration falls above the line extending downward from a serum concentration of 150 mg/L (993 mmol/L) at 4 hours after the time of ingestion.[18] In two of the four individual case reports, the patient's first serum paracetamol concentration was below the nomogram treatment line and a subsequent serum concentration was above the treatment line. Bizovi et al.[13] described a 25-year-old woman whose paracetamol concentration at 6 hours after ingestion of Tylenol® Extended Relief was 70 mg/L (463 μmol/L, below the treatment line) and at 14 hours postingestion her serum concentration was 160 mg/L (1059 μmol/L), which falls above the treatment line. This patient also ingested liquid Nyquil® (paracetamol IR, dextromethorphan, doxylamine and pseudoephedrine). The patient recovered uneventfully with acetylcysteine treatment.

Vassallo et al.[14] reported a 17-year-old woman who ingested paracetamol SR 13g alone. Her serum paracetamol concentration at 5 hours was below the treatment line. Oral acetylcysteine was initiated when her 11-hour serum concentration was 80 mg/L (529 μmol/L). Liver function tests remained within the normal range. Graudins et al.[15] described a 13-year-old girl who ingested an unknown amount of paracetamol SR. Her serum paracetamol concentration was 89 mg/L (589 μmol/L) upon presentation (19 hours after ingestion). The patient developed liver injury but recovered with acetylcysteine treatment.

Lystbaek and Norregaard[16] described a 22-year-old woman in Denmark who ingested paracetamol IR 4g, 50 phenobarbital tablets and an unknown

1 The use of trade names is for product identification purposes only and does not imply endorsement.

quantity of metoprolol and zopiclone. The paracetamol concentration was undetectable 4 hours after admission and her ALT level was normal. The patient left medical care against the advice of her physician and was readmitted in 48 hours after an additional ingestion of paracetamol SR 6g, paracetamol IR 4g and 15 zopiclone tablets. Treatment with acetylcysteine was started but discontinued after the serum paracetamol concentration was returned as 74 mg/L (490 μmol/L). A subsequent serum level at 13 hours postingestion was 47 mg/L (311 μmol/L), but acetylcysteine was not resumed. Her initial ALT level was 968 IU/L, which rose to 3718 IU/L. The patient died 8 days later from fulminant hepatic failure.

Cetaruk et al.[17] reported a series of 13 patients presenting for treatment following paracetamol SR overdose, including three patients who had initial paracetamol concentrations below the treatment line used in the US but later had concentrations above this line (figure 1). However, the initial paracetamol samples for these three patients were obtained <4 hours after ingestion. Only one of these three patients reported coingestants. Ten of the 13 patients were treated with acetylcysteine and all 13 recovered without clinical or laboratory evidence of liver injury. The authors suggested an additional paracetamol concentration should be collected at least 4–6 hours after the first, assuming the first concentration reading is obtained within 4–8 hours postingestion, and that a full course of acetylcysteine treatment be given if either concentration is above the treatment line.

2.2 Poison Centre Database

A search of the AAPCC TESS database yielded 3003 cases from 1994 to 2002 in which a paracetamol SR product was identified. The number of

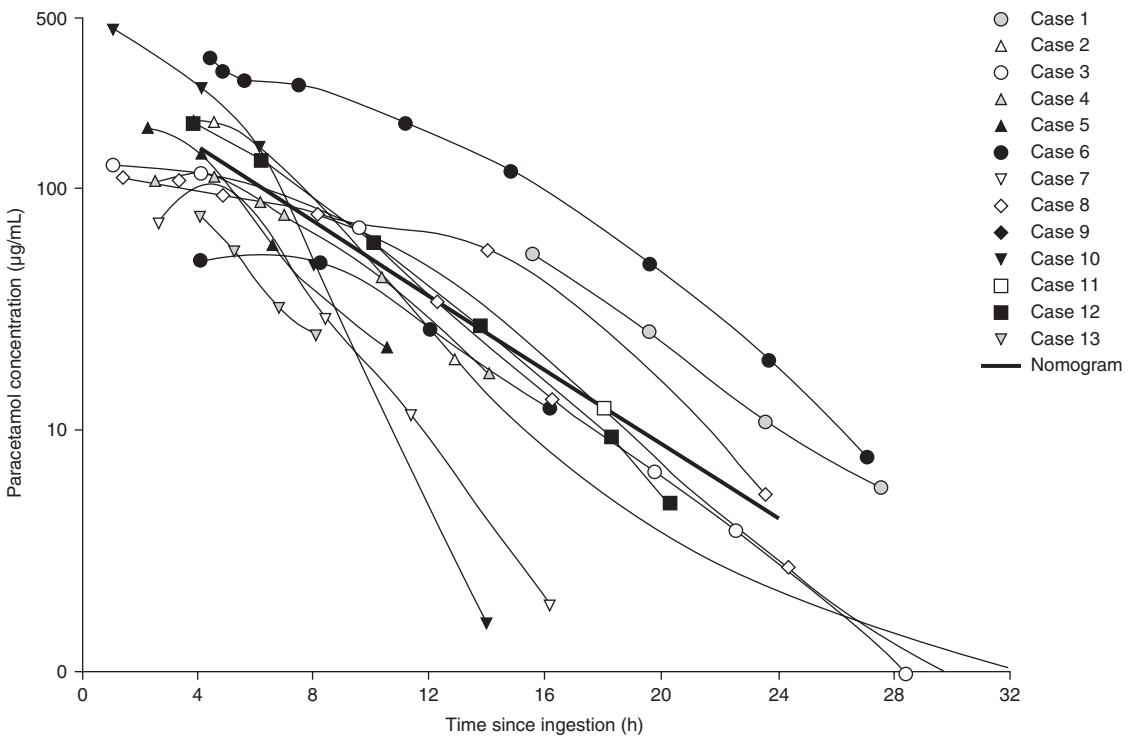

Fig. 1. Serum paracetamol (acetaminophen) concentrations in patients following sustained release paracetamol overdose.[17] The 'possible toxicity' line of the Rumack-Matthew nomogram is included for comparison (10 μg/mL = 66.16 μmol/L). Three patients (cases 3, 8 and 11) whose initial serum paracetamol concentration was below the nomogram line but a subsequent concentration was above the line are shown. Reproduced from Cetaruk,[17] with permission from American College of Emergency Physicians.

Table II. Number of exposure cases with sustained release (SR) and immediate release (IR) paracetamol (acetaminophen) reported in the Toxic Exposure Surveillance System database and corresponding US sales data (1994–2002)

Parameter	1994	1995	1996	1997	1998	1999	2000	2001	2002
No. of paracetamol SR cases	0	0	164	535	183	325	374	681	741
No. of paracetamol IR[a] cases	25 685	27 586	28 732	27 945	26 585	25 653	27 635	28 310	29 226
Paracetamol SR cases, proportion of total paracetamol cases (%)	NA	NA	0.57	1.9	0.69	1.3	1.4	2.4	2.5
Sales of paracetamol SR ($\times 10^8$)	0.76	1.9	2.9	2.5	2.5	5.2	5.4	5.8	6.4
Sales of paracetamol IR[b] ($\times 10^8$)	67.9	60.4	94.0	95.9	95.9	95.0	88.8	85.9	79.0
Sales of SR, proportion of total paracetamol sales (%)	1.1	3.1	3.0	2.6	2.6	5.2	5.7	6.3	7.5

a Adult paracetamol products taken alone (no coingestants).

b Adult paracetamol products only (excludes paediatric preparations and combination products).

NA = not applicable.

human exposure cases involving paracetamol SR increased by 450% from 1996 to 2002 (table II), while the number of IR cases increased by only 14%. Expressed as a proportion of all paracetamol (adult formulations) cases, SR cases increased from 0.6% in 1996 to 2.5% in 2002. During the same period, sales of paracetamol SR tablets increased by 220% and SR tablet sales as a proportion of total paracetamol tablet sales increased from 3% in 1996 to 7.5% in 2002. Patient demographics and call characteristics for cases involving the SR formulation are provided in table III.

In US poison centres, the information specialist (typically a specially trained nurse or pharmacist) assigns several classifications to all cases. Cases are categorised by intent (unintentional, intentional), pattern (acute ingestion, acute-on-chronic, chronic), relation of clinical effects to the reported exposure (related, unrelated, relationship unknown) and medical outcome (no effect, minor, moderate, major, death), among others. The category of intentional ingestion is subcategorised as suicide, intentional misuse, etc.

In the TESS database, intentional exposure accounted for 37% of SR cases while unintentional exposures accounted for 60% (table IV). Suspected suicidal intent was the most common type of intentional exposure (77%), followed by intentional misuse, for example overuse to relieve pain (18%). The distribution of reasons for SR formulation cases differs from that of all adult paracetamol IR formulation cases reported in the AAPCC annual reports during the same time period. Cases involving paracetamol SR were more likely to be unintentional exposures and less likely to be associated with an intentional exposure than cases involving the IR formulation.

Of the 3003 paracetamol SR human exposure cases, 2596 (86%) were acute exposures (a single, repeated or continuous exposure occurring over a period of ≤8 hours). Acute-on-chronic exposures accounted for 227 (8%) cases (a single exposure that was preceded by a continuous, repeated or intermittent exposure occurring over a period of >8 hours). Chronic exposures accounted for 147 (5%) cases. The remaining 33 cases were of unknown duration.

Table III. Patient demographics and case characteristics involving sustained release paracetamol (acetaminophen) products reported in the Toxic Exposure Surveillance System database (1994–2002) [n = 3003]

Characteristic	No. of cases (%)
Patient demographics	
Age (y)	
0–12	789 (26.3)
13–19	541 (18.0)
20–29	428 (14.3)
30–39	275 (9.2)
40–49	216 (7.2)
50–59	125 (4.2)
60–69	147 (4.9)
>70	351 (10.9)
unknown	131 (4.4)
Female	1983 (66.0)
Pregnant	11 (<1)
Number of substances reported	
One	2106 (70.1)
Two	593 (19.7)
Three or more (3–12)	304 (10.1)

Table IV. Comparison of exposure reasons for sustained release (SR) and immediate release (IR) paracetamol (acetaminophen) formulations reported in the Toxic Exposure Surveillance System database (1994–2002)

Category	Paracetamol SR cases [no. (%)]	Paracetamol IR cases[a] [no. (%)]
Unintentional exposures		
all	1813 (60.4)	91 863 (47.3)
general	907	NA
therapeutic error	791	NA
misuse	101	NA
bite/sting	3	NA
environmental	2	NA
unknown	9	NA
Intentional exposures		
all	1098 (36.6)	99 334 (51.2)
suspected suicidal	846	NA
misuse	202	NA
abuse	22	NA
unknown	28	NA
Adverse reactions related to paracetamol SR	81 (2.7)	2024 (1.0)
Other	2 (<0.1)	115 (0.1)
contaminant/tampering	2	NA
Unknown reason for exposure	9 (0.3)	750 (0.4)
Total	**3003 (100)**	**194 086 (100)**[b]

a Adult paracetamol products taken alone (no coingestants).

b Of the 247 375 IR exposure cases in the Toxic Exposure Surveillance System database, this number had an exposure reason reported.

NA = not applicable.

The TESS database only records those clinical effects that were reported and may be limited in that additional clinical effects may have been present but not reported. Overall, 921 (31%) of the 3003 patients had at least one clinical effect recorded.

Thirty percent of all cases reported an exposure to substances in addition to paracetamol; therefore, the reported clinical effects associated with these cases may not be related to paracetamol. Of the 2106 patients that reported an exposure to paracetamol SR and no other substances, 481 (23%) patients reported at least one clinical effect. The total number of clinical effects reported was 924, of which 599 (65%) were classified as related to the exposure. The most common types of related clinical effects were gastrointestinal (vomiting, nausea, abdominal pain) and hepatic (elevated serum transaminase levels or prolonged prothrombin time). Neurological effects (lethargy, agitation, slurred speech) and other miscellaneous effects such as fever, diaphoresis and general pain were typically deemed not to be related to the reported exposure. The relationship to the reported exposure was unknown in 125 clinical effects (table V).

Table VI provides more specific data for the gastrointestinal and hepatic clinical effects related to treatment. These two categories account for 80% of all related clinical effects reported in association with paracetamol SR exposures. The majority (82%) of these related clinical effects followed an intentional exposure and 17% of the effects followed an unintentional exposure.

In the TESS database, cases are recorded as either followed to a known outcome (medical outcome-followed: the case is followed and outcome documented) or as not followed to a known outcome (medical outcome-not followed: the case was not followed but is assigned an outcome decision judged upon the reported exposure). Of the paracetamol SR human exposure cases, 1370 cases (45.6%) were followed to a known medical outcome and 1492 cases (49.7%) were not followed. Cases that are not followed are typically those involving exposure to small amounts of the drug. The remaining 141 cases

(4.7%) were classified by the poison centre staff as unrelated to the reported exposure.

Overall, 60% of the 1370 cases followed to a known outcome had no effect following exposure. Another 26% reported minor effects, 11% reported moderate effects and 3% reported major effects. Two cases resulted in death and are discussed next. Acute exposures accounted for 88% of the followed outcomes, 6% were acute-on-chronic exposures and 4% were chronic exposures. The number of acute-on-chronic and chronic exposures is much smaller than the acute group and the distribution (percentage) of medical outcomes differs slightly between the groups. Over 60% of acute exposures did not result in any medical effect, while acute-on-chronic and chronic exposures tended to result more often in a minor or moderate medical effect. Also, no deaths were associated with an acute exposure, while one death was reportedly associated with an acute-on-chronic exposure and one with a chronic exposure.

Two deaths in the TESS data set occurred in patients who were receiving paracetamol SR (table VII). Because of limitations of the data, the cause of these deaths cannot be confirmed as exposure to paracetamol SR. These deaths were reported as exposure cases that included paracetamol SR as well as other substances. A 71-year-old man, with a history of chronic alcohol abuse and binge drinking, ingested 1300–1950mg of paracetamol SR every 2–3 hours for 1 week. The ingestion was classified as chronic and the reason for exposure was intentional misuse. Upon arrival at the emergency department, his ethanol concentration was <10 mg/dL and paracetamol concentration was 197 μg/mL, he had an AST level of 5712 IU/L, ALT level of 7494 IU/L and international normalised ratio of 7. The reported clinical findings included multiple cardiovascular, gastrointestinal, hepatic, neurological, respiratory and renal effects. The patient was administered oral acetylcysteine, intravenous fluids and vitamin K. Duration of therapy and interval from ingestion to treatment were not reported. Life support was withdrawn 24 hours after admission.

A 36-year-old man was found in a hotel room with empty bottles of paracetamol SR, carbamazepine and diphenhydramine. Although the exact amount ingested of each substance is not certain, the maximum amount possible was reported as 50 tablets of paracetamol SR, 30 tablets of carbamazepine and 24 tablets of diphenhydramine. At the time of admission, his paracetamol concentration was 162 μg/mL with a carbamazepine concentration of 34.4 μg/mL. Over the next several days the patient developed evidence of hepatic failure with an AST level of 6504 IU/L and an ALT of 11 189 IU/L. The multiple clinical effects reported included cardiovascular, dermal, gastrointestinal, hepatic, neurological and respiratory findings. Although acetylcysteine was administered, the duration of treatment and interval from ingestion to treatment were not reported. The patient died on his sixth hospital day.

The medical outcomes of all paracetamol SR and IR exposures that were followed are compared in table VIII. There does not appear to be a difference in medical outcome of those patients exposed to paracetamol SR compared with those exposed to paracetamol IR, including instances of death ($p > 0.05$).

Table V. Relationship of clinical effects to reported exposure of sustained release paracetamol (acetaminophen) only (no other substances recorded) reported in the Toxic Exposure Surveillance System database (1994–2002)

Clinical effect	Clinical effect relation to reported exposure			
	related [no. (%)]	not related [no. (%)]	unknown [no. (%)]	total
Gastrointestinal	356 (77)	44 (10)	62 (13)	462
Hepatic	121 (95)	6 (5)	0	127
Neurological	50 (36)	57 (42)	30 (22)	137
Cardiovascular	11 (27.5)	20 (50)	9 (22.5)	40
Dermatological	9 (35)	12 (46)	5 (19)	26
Renal	4 (100)	0	0	4
Respiratory	1 (33)	1 (33)	1 (33)	3
Ocular	1 (50)	1 (50)	0	2
Miscellaneous	46 (37)	59 (48)	18 (15)	123
Total	**599 (65)**	**200 (22)**	**125 (13)**	**924 (100)**

3. Conclusions

3.1 Adverse Effects from Therapeutic Doses

Since its introduction in 1994, the SR formulation of paracetamol has captured a progressively greater portion of paracetamol sales. Concurrently, there has been an increase in reported exposures to paracetamol SR in the medical literature and in the AAPCC surveillance network. An increase in reports in proportion with increasing sales would be expected. Surprisingly, the proportion of reports to the AAPCC TESS associated with the SR formulation is much lower than its proportion of paracetamol sales.

Paracetamol is known to be a remarkably safe analgesic when used appropriately. However, when used in doses that are higher than recommended, liver injury can occur. Therefore, the relative safety of each type of use, therapeutic or greater than therapeutic, is an important consideration. Since each tablet of the SR formulation contains a larger amount of paracetamol, the potential risk for adverse effects from the same number of pills may be greater with a SR preparation than with an IR preparation.

The information available indicates that the adverse event and safety profile of paracetamol SR during therapeutic use is very similar to IR formulations of paracetamol. During therapeutic use, minor effects such as gastrointestinal upset and headache may occur although interpretation of data from those studies that were not placebo controlled is difficult. The rate of these effects varies substantially between the different pain models but overall does not appear to be different between the SR and IR formulations of paracetamol.

3.2 Toxicity and Management of Overdose

The medical literature indicates that overdose with paracetamol SR may cause liver injury very similar to the injury induced by IR formulations. However, no cases of unusual types of toxicity have been associated with the SR formulations and no deaths have been reported from an overdose of paracetamol SR alone based on this comprehensive review.

The information available concerning management of a paracetamol overdose is also difficult to evaluate. In general, both the medical literature and the TESS database indicate that the management of overdose is similar for IR and SR formulations. In theory, gastrointestinal decontamination could be effective for a greater period postingestion in the case of the SR formulation.[19] However, this potential has not been studied.

As in overdose from the IR preparation, the approach to management of a SR overdose has been to measure the serum paracetamol concentration in order to stratify the risk of hepatic toxicity. The tool used for this assessment, the Rumack-Matthew nomogram, is well established for paracetamol IR and

Table VI. Exposures to sustained release paracetamol (acetaminophen) only and related clinical effects – specific gastrointestinal and hepatic effects by reason for exposure reported in the Toxic Exposure Surveillance System database (1994–2002)

Reported effect	Unintentional [no. (%)]	Intentional [no. (%)]	Other[a] [no. (%)]	Total
Gastrointestinal	65 (18)	285 (80)	6 (2)	356
vomiting	27	136	1	164
nausea	25	85	4	114
abdominal pain	7	56	1	64
other	6	8	0	14
Hepatic	14 (11)	105 (87)	2 (2)	121
AST/ALT high level elevation (>1000 U/L)	3	28	0	31
AST/ALT low level elevation (>100 but ≤1000 U/L)	5	27	0	32
prolonged PT	2	25	1	28
other LFT abnormality	2	11	0	13
bilirubin level increase	1	12	1	14
other coagulopathy	1	2	0	3

a Includes adverse reactions, other and unknown exposure reasons.

LFT = liver function test; **PT** = prothrombin time.

Table VII. Summary of death reports associated with sustained release (SR) paracetamol (acetaminophen) products reported in the Toxic Exposure Surveillance System database (1994–2002)

Characteristic	Death 1	Death 2
Sex, age (y)	Male, 71	Male, 36
Exposure site	Own residence	Other residence
Reason for exposure	Intentional/misuse	Intentional/suspected suicidal
Type of exposure	Chronic	Acute-on-chronic
Number of substances ingested	Two: paracetamol SR, alcohol	Three: paracetamol SR, carbamazepine, diphenhydramine
Quantity of substances	Paracetamol SR 1300–1950mg every 2–3h (around the clock) for 1wk	Maximum possible: 50 tablets paracetamol SR, 30 tablets carbamazepine, 24 tablets diphenhydramine
Clinical effects reported	Cardiovascular, gastrointestinal, hepatic, neurological, renal, respiratory	Cardiovascular, gastrointestinal, hepatic, neurological, renal, respiratory, dermatological
Laboratory results	At admission: paracetamol 197 μg/mL alcohol <10 mg/dL AST 5712 IU/L ALT 7494 IU/L INR 7	At admission: paracetamol 162 μg/mL carbamazepine 34.4 μg/mL Over next several days: AST 6504 IU/L ALT 11 189 IU/L
Interventions	IV fluids, intubation, oxygen, phytonadione, vasopressor, acetylcysteine (oral)	IV fluids, activated charcoal (single dose), lavage, acetylcysteine (oral)

INR = international normalised ratio; **IV** = intravenous.

requires a serum paracetamol concentration to be drawn between 4 hours and 24 hours after the time of ingestion.[20] Owing to the SR nature of the new formulation, investigators were aware of the potential for 'nomogram crossers' – patients whose initial paracetamol concentration was below the treatment line but subsequently rose above this nomogram line, and identified such cases.[13,14,17]

Currently, some investigators and the manufacturers of paracetamol SR formulations recommend a second serum paracetamol concentration be drawn following an overdose of the SR formulation, if the first reading was below the treatment line. If the second concentration rises above the line, the patient should receive treatment with acetylcysteine. The limited data available indicate that this technique is effective; however, it does not establish that it is necessary. To date, there has not been a case reported in which a 'late crosser' was not treated with acetylcysteine; therefore, we do not know whether toxicity would develop in these cases.

In response to a case presented by Graudins et al.,[15] representatives from the manufacturer of paracetamol SR in the US (McNeil Consumer and Specialty Pharmaceuticals) have provided expanded recommendations for patients who overdose on paracetamol SR and for those in whom the substance ingested is unknown.[20] These recommendations include an initial paracetamol concentration assessment collected at least 4 hours postingestion, with a subsequent concentration obtained 4–6 hours later. If either value is above the treatment line, then a full course of acetylcysteine treatment should be administered. Yet another concentration reading is indicated if the second value is higher than the first or lies close to the treatment line.

Table VIII. Outcome associated with exposure to sustained release (SR) paracetamol (acetaminophen) vs immediate release (IR) paracetamol-followed medical outcomes reported in the Toxic Exposure Surveillance System database (1994–2002)

Formulation	No. of exposures (%)	p-Value	Relative risk (95% CI)
Minor effect			
SR	358 (26)	0.190	0.94 (0.86, 1.03)
IR	28 877 (28)		
Moderate effect			
SR	147 (20)	0.404	0.94 (0.80, 1.09)
IR	11 928 (11)		
Major effect			
SR	44 (3)	0.727	1.05 (0.79, 1.41)
IR	3175 (3)		
Death			
SR	2 (0.1)	0.307	0.49 (0.12, 1.97)
IR	309 (0.3)		

3.3 Limitations

There are limitations to our analysis. A publication may not distinguish between IR and SR forms when addressing the treatment of paracetamol poisoning. Another issue is the lack of specific safety information. A large proportion of adverse events that are reported in the literature do not specify the severity of the event or the treatment group in which they occurred. T'he only death reported in the medical literature associated with an SR product also involved an IR formulation and from the authors description, the antidote was not used in the normal manner. Acetylcysteine treatment was discontinued prematurely and was not restarted despite a paracetamol concentration at 13 hours' postingestion that was above the nomogram treatment line.[16]

Surprisingly, no paracetamol SR-related exposure cases were recorded in the TESS database for 1994 or 1995. It appears that because of system issues, the code for the product may not have been available to poison centres.

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