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Database evaluation of paracetamol concentrations in a toxicology laboratory in Toruń, Poland, 2018–2022

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ABSTRACT
Paracetamol is a commonly used and easily accessible drug with antipyretic and analgesic properties. Its overdose leads to severe liver failure. In diagnostic procedures, an important role is played by the determination of paracetamol concentration in blood serum, which not only confirms poisoning but also helps assess the risk of hepatotoxicity. The aim of this study was to retrospectively analyze the data on paracetamol concentration tests performed at the Toxicology Laboratory of the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń between 2018–2022. The serum of patients suspected of poisoning was tested using the immunoassay method. The study demonstrated an upward trend in the number of paracetamol concentration tests performed. It was observed that the highest percentage of patients were female, and the largest age group ranged 3–17 years old. The positive paracetamol concentrations most often fell within toxic levels and were most frequently obtained from female patients.
Keywords: paracetamol; acetaminophen; immunoassay; ethanol.

INTRODUCTION

Paracetamol is one of the most popular and frequently used painkillers and antipyretics in the world. It is the drug of choice for people who cannot be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), such as those with bronchial asthma, peptic ulcer disease, haemophilia, children under the age of 12, and pregnant or breastfeeding women. It is also used in cases of allergy to salicylates. In Poland, paracetamol is available without a prescription as a single or multicomponent therapeutic agent [1, 2].

This compound was first synthesized in 1878 by Harmon Northrop Morse, who reduced p-nitrophenol using tin in glacial acetic acid. However, it became widely used as a medicine only after the researcher had passed away. The product was first sold in 1955 by McNeil Laboratories as a pain reliever and antipyretic for children. In 1956, 500 mg paracetamol tablets were introduced for sale in the UK, initially available only by prescription, serving as painkillers and antipyretics. Unlike other painkillers containing aspirin, paracetamol did not irritate the stomach [3].

Despite the drug's popularity, the mechanism of paracetamol's effect on pain and fever remains a matter of debate. Unlike NSAIDs, paracetamol does not have prominent anti-inflammatory activity and does not inhibit the blood clotting process. The drug's effect is believed to result from the activation of descending serotonergic pathways. It is reasonable to assume that while the *in vivo* effect is similar to that of selective cyclooxygenase-2 (COX-2) inhibitors, it differs from the effect observed with NSAIDs. Paracetamol also inhibits prostaglandin synthesis in the central nervous system [4, 5].

Paracetamol is mainly metabolized in the liver. Phase I reactions occur through oxidation, reduction, and hydrolysis, producing polar drug metabolites. Phase II reactions, known as conjugation reactions (e.g., with glucuronic acid or sulfate), usually detoxify the metabolites and involve interactions between the polar phase I metabolite groups and conjugation groups. The end products, which are inactive and non-toxic, are ultimately excreted by the kidneys. Oxidative reactions typically involve cytochrome P450, nicotinamide adenine dinucleotide phosphate oxidase (NADPH), and oxygen, leading to the formation of a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is primarily responsible for the hepatotoxicity of paracetamol [6].

The first case of paracetamol poisoning was reported in 1966. Within 10 years, antidotes were developed, and by 1980, acetylcysteine (NAC) was considered the optimal antidote for treating poisonings. In the 40 years since paracetamol was introduced to the market, paracetamol poisoning has become a common cause of emergency hospitalization. The toxic effects of paracetamol are observed in several scenarios: after a single excessive ingestion as an intentional suicidal attempt, after accidental ingestion (usually by a child), or, rarely, by intentional administration by a third party. Paracetamol poisoning can also occur through repeated excessive consumption in an attempt to control medical ailments such as toothache [7]. In Europe, North America, and Australia, paracetamol remains the leading pharmaceutical cause of overdose poisoning. It is a relatively common health problem and the most frequent contributor to acute liver failure in many countries. The broad availability of paracetamol has made it one of the most widely

taken drugs. It is estimated that paracetamol is involved in 6% of global poisonings [8, 9]. Between 2000–2018, U.S. poison control centers reported an increase in cases involving all over-the-counter (OTC) pain medications that resulted in serious medical consequences or the need for hospital admission. Acetaminophen was responsible for 48.0% of cases and 64.5% of deaths [10]. According to the literature, a paracetamol concentration of >20 µg/mL is toxic, and ≥160 µg/mL is lethal [11].

The aim of the study was to retrospectively analyze the results of toxicological tests on paracetamol concentrations in the serum samples of patients diagnosed and treated in hospital wards in Kuyavian-Pomeranian Voivodeship in 2018–2022. The analysis also included cases in which ethanol concentration was determined at the same time.

MATERIALS AND METHODS

The analysis focused on 362 paracetamol concentration results. The calculations were based on results from samples taken 4 h after drug administration. Paracetamol concentration was determined using the Thermo Scientific™ Indiko Plus immunological analyzer and a dedicated set of DRI Acetaminophen Serum Toxicology Assay reagents (measurement range 2.5–200 µg/mL; samples above this range were diluted and re-assayed). The ethyl alcohol concentration results were obtained using headspace gas chromatography with the Shimadzu GC2010 Plus and HS-20 (limit of detection – LOD: 0.1 g/L, limit of quantitation – LOQ: 0.2 g/L). Validation parameters of the acetaminophen test are available on the Thermo Scientific official website [12]. Both methods are controlled using Internal and External Quality Control. The tests were conducted in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland (ZDL WSzZ in Toruń). The material used for assessing paracetamol concentration was serum, while ethanol content was measured using whole blood collected in test tubes containing lithium heparin. The data on the age and gender of patients came from the hospital's IT system and from the information included in the referrals for the toxicological tests. MS Excel program was used for calculations.

RESULTS

The acquired results were presented in the form of charts and tables.

2018–2022

Over the past few years, there has been an upward trend in the number of paracetamol concentration tests. During this period, the highest number of tests was performed in 2022, while the fewest were conducted in 2018 (Fig. 1). Women accounted for 70% (254 tests) of all suspected cases of paracetamol poisoning, while men accounted for 30% (108 tests). The results were divided into the following age groups: 0–2 years old, 3–17 years old, 18–64 years old, and over the age of 65. One patient was not classified into any of these groups due to missing information on the referral. The largest number of tests, 209, were performed on patients aged 3–17. Only 8 paracetamol concentration tests were carried out on patients over 65 years old.

There were 278 positive paracetamol concentration tests. Tests exceeding a concentration of 20 µg/mL were much more common in female patients (women: 141 results, men: 41 results) – Figure 2. Paracetamol concentrations between 20–100 µg/mL were observed in 96 women and 33 men, concentrations between 100–160 µg/mL in 28 women and 3 men, and fatal concentration levels in 17 women and 5 men. The average concentration in samples that exceeded 20 µg/mL was 85 µg/mL, the median was 61.5 µg/mL, and the maximum value was 399.6 µg/mL (in a 30-year-old male patient, the result obtained in 2022). Toxic concentrations constituted 65% of the positive results, i.e., results above the cut-off point. In women, such results accounted for 70% of tests, while in men, they accounted for 51% of tests.

The number of simultaneously ordered tests for the concentration of paracetamol in serum and ethyl alcohol in the blood of patients suspected of poisoning was also analyzed. Among the 89 tests ordered for these 2 parameters, positive results were obtained in 14 cases (paracetamol ≥2.5 µg/mL and ethanol ≥0.2 g/L) – Table 1. In this group, the highest ethyl alcohol concentration was 2.99 g/L, and the highest paracetamol concentration was 317 µg/mL – Table 2.

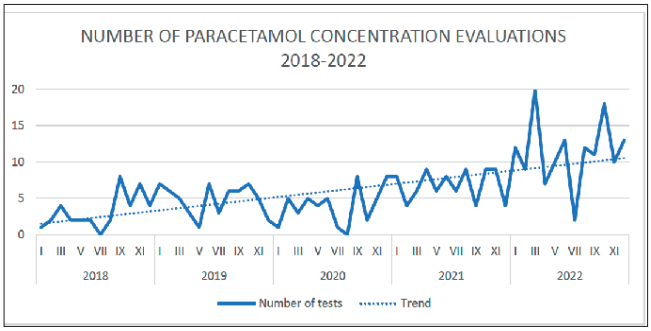
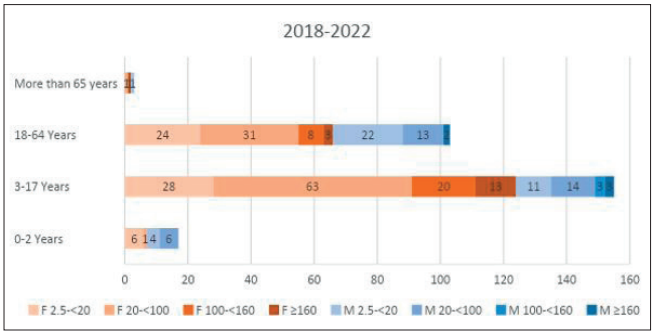


FIGURE 1. Number of paracetamol concentration evaluations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2018–2022



F – female; M – male

FIGURE 2. Number of paracetamol concentration evaluations (positive results) in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2018–2022, divided by sex, age, and concentration (µg/mL)

TABLE 1. Number of simultaneously ordered determinations of paracetamol and ethyl alcohol concentrations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2018–2022

Test	Year					Total
	2018	2019	2020	2021	2022	
Paracetamol + ethanol (in all)	7	12	15	18	37	**89**
Paracetamol ≥2.5 µg/mL + ethanol ≥0.2 g/L	1	3	0	2	8	**14**

TABLE 2. Summary of detailed data for patients in the group with both paracetamol concentrations ≥2.5 µg/mL and ethanol concentrations ≥0.2 g/L

Year	Gender	Age (years)	Paracetamol concentration (µg/mL)	Ethanol concentration (g/L)
2018	M	39	22.0	2.99
2019	F	14	61.0	1.20
		20	3.0	1.23
	M	43	5.0	1.84
2021	F	20	317.0	0.46
	M	29	4.9	1.98
2022	F	14	3.5	1.66
		22	3.7	2.25
		51	10.1	2.85
	M	25	68.1	0.65
		26	62.5	0.45
		28	5.0	2.99
		46	9.2	0.39
		62	43.8	1.18

F – female; M – male

2018

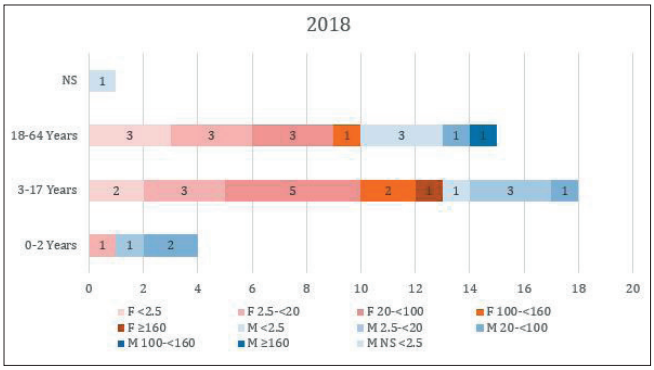
In 2018, 24 paracetamol concentration tests were conducted on women, 13 tests on men, and 1 test was conducted where the gender and age of the patient were not specified. In the 0–2 years age group, 4 tests were performed, 18 tests in the 3–17 age group, 15 tests in the 18–64 age group, and 1 test in the non-specified age group. No tests were performed in the >65 years age group that year.

Analyzing the results in terms of the obtained concentrations, the following were found: <2.5 µg/mL – 10 tests, 2.5–20 µg/mL – 11 tests, 20–100 µg/mL – 12 tests, 100–160 µg/mL – 3 tests, and ≥160 µg/mL – 2 tests (Fig. 3).

2019

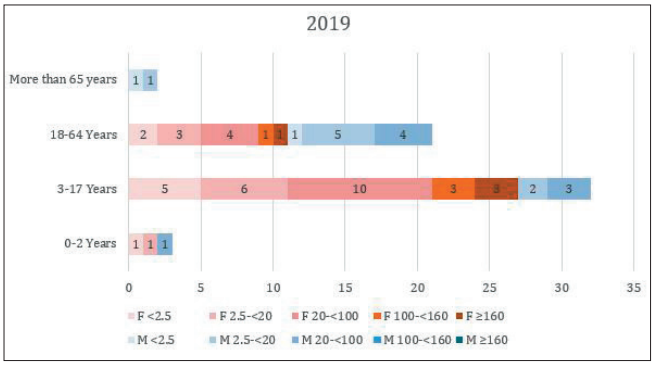
In 2019, paracetamol tests in women accounted for 40 tests, and in men for 18 tests. Most of these tests were performed in the 3–17 age group (32 tests), while the fewest were conducted in patients over 65 years of age (2 tests) and in the 0–2 years age group (3 tests).

The following results were obtained when analyzing the concentrations: <2.5 µg/mL – 10 tests, 2.5–20 µg/mL – 18 tests, 20–100 µg/mL – 22 tests, 100–160 µg/mL – 4 tests, and ≥160 µg/mL – 4 tests (Fig. 4).



F – female; M – male; NS – non-specified

FIGURE 3. Number of paracetamol concentration evaluations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2018, divided by sex, age, and obtained concentration (µg/mL)



F – female; M – male

FIGURE 4. Number of paracetamol concentration evaluations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2019, divided by sex, age, and obtained concentration (µg/mL)

2020

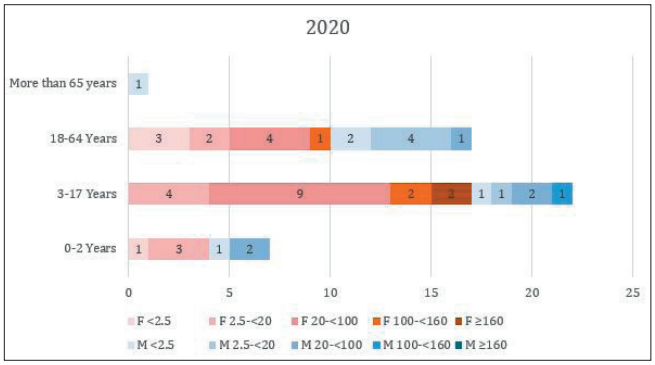
In 2020, paracetamol tests in women accounted for 31 determinations, and in men for 16 determinations out of all analyses of this parameter. It was found that 7 tests were performed in the 0–2 age group, 22 in the 3–17 age group, 17 in the 18–64 age group, and the fewest tests were conducted in patients over 65 years of age – 1 test (Fig. 5).

The ranges of obtained paracetamol concentrations were as follows: <2.5 µg/mL – 9 tests, 2.5–20 µg/mL – 14 tests, 20–100 µg/mL – 18 tests, 100–160 µg/mL – 4 tests, and ≥160 µg/mL – 2 tests (Fig. 5).

2021

As in previous years, in 2021, the vast majority of paracetamol tests were performed on women, accounting for 63 tests.

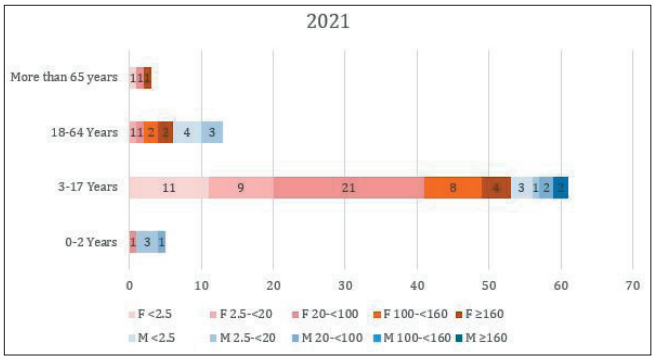
Analyses conducted on men accounted for 19 tests. Examining the results across various age groups, it was found that: in the 0–2 age group, 5 tests were performed; in the 3–17 age group, 61 tests; in the 18–64 age group, 13 tests; and the lowest number of tests were conducted on patients over 65 years of age, with 3 tests.



F – female; M – male

FIGURE 5. Number of paracetamol concentration evaluations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2020, divided by sex, age, and obtained concentration (µg/mL)

The following results were acquired when analyzing the obtained concentrations of the drug: <2.5 µg/mL – 19 tests, 2.5–20 µg/mL – 17 tests, 20–100 µg/mL – 27 tests, 100–160 µg/mL – 10 tests, and ≥160 µg/mL – 9 tests (Fig. 6).



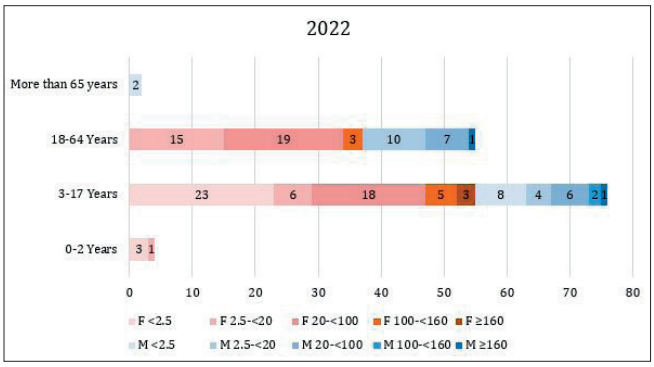
F – female; M – male

FIGURE 6. Number of paracetamol concentration evaluations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2021, divided by sex, age, and obtained concentration (µg/mL)

2022

In 2022, the number of women among the patients tested was 96, while men accounted for 41 tests. Regarding the age groups, the following results were found: 0–2 age group – 4 tests, 3–17 age group – 76 tests, 18–64 age group – 55 tests, and the lowest number of tests were performed on patients over 65 years of age – 2 tests (Fig. 7).

The following results were obtained when analyzing the concentrations of the drug: <2.5 µg/mL – 36 tests, 2.5–20 µg/mL – 36 tests, 20–100 µg/mL – 50 tests, 100–160 µg/mL – 10 tests, and ≥160 µg/mL – 5 tests (Fig. 7).



F – female; M – male

FIGURE 7. Number of paracetamol concentration evaluations in the Toxicology Laboratory of the Department of Laboratory Diagnostics at the Ludwik Rydygier Provincial Polyclinic Hospital in Toruń, Poland, in 2022, divided by sex, age, and obtained concentration (µg/mL)

DISCUSSION

Over the period of 2018–2022, an increase in the number of patients both suspected of and intoxicated with paracetamol has been reported. In this study, 65% of positive tests resulted in concentration values considered toxic. A long-standing trend of overdose cases has also been indicated by researchers from Pomerania and Lesser Poland [13, 14]. It is worth emphasizing that women were most often suspected of paracetamol poisoning – they accounted for 70% of all patients tested for paracetamol concentration and 77% of all toxic-level results. Similar results were obtained in hospitalized patients from the Pomeranian Toxicology Center [13], where the percentage of poisonings was also higher in women. The results concerning patient gender are also reflected in analyses by researchers from other countries [8, 15, 16]. Female patients were the dominant gender in cases of paracetamol concentrations ≥20 µg/mL in patients up to 18 years of age, accounting for 79% (97 tests). Similar results were reported by Kominek et al. from the Medical University in Lublin in 2015, which noted an increase in the percentage of girls intoxicated with paracetamol [17]. The results of Sosnowska et al. (Clinical Department of Toxicology and Cardiology in Stefan Wyszyński Regional Specialist Hospital in Lublin, 2022) also indicate that more female adolescent patients were hospitalized due to paracetamol intake [18].

In this study, when considering results by patient age, it should be noted that the vast majority of tests were performed on patients aged 3–17, and this group was dominant in terms of toxic concentration levels. The second-largest group consisted of patients aged 18–64. This confirms the trend of paracetamol use by children and adolescents observed over recent years, not only in Poland but also worldwide [16, 19, 20]. In this younger group, the number of tests for paracetamol concentration significantly increased in the last analyzed year. It should be noted that the only decrease in the number of evaluations, compared to the previous year, occurred in 2020, likely due to limited access to medical services during the COVID-19 pandemic.

The suspected paracetamol poisonings were most often observed in the spring and autumn seasons, likely related to the occurrence of various infections in Poland during these months. In neonates and infants (up to 2 years of age), there were 7 cases of toxic paracetamol concentrations out of 23 tests conducted. Available literature suggests that children are less sensitive to acute paracetamol intoxication due to a larger liver size relative to body weight and larger glutathione stores compared to adults [21, 22]. It's also worth mentioning that in children, the contribution of specific metabolic pathways varies with age: the process of sulfation is more common than glucuronidation in children under 9 years old, and oxidation (related to P450, especially CYP2E1) plays a minimal role in neonates. CYP2E1 activity increases with age, reaching maturity between 1–10 years old. This may affect the compound's toxicity in children. Low or absent CYP2E1 in young children results in low amounts or absence of NAPQI, hence the risk of hepatotoxicity in very young children is lower than in adult patients [1, 23].

Indications for paracetamol determination included both suspicion of poisoning alone and suspicion of combined poisoning, which explains the presence of low concentrations (<2.5 μg/mL) in some results. In such cases, paracetamol was excluded as the cause of poisoning. The study also analyzed cases in which simultaneous consumption of paracetamol and ethyl alcohol was suspected. In the group of patients with positive results for both parameters, 6 cases showed toxic levels of paracetamol. In most of these patients, the level of alcohol intoxication did not exceed 1.2 g/L, except for 1 patient with a blood ethanol concentration of 2.99 g/L and a paracetamol concentration of 22 μg/mL. Conversely, the patient in this group with the highest paracetamol concentration (317 μg/mL) had an ethanol concentration of 0.46 g/L. There was no significant gender difference in patients who tested positive for both ethyl alcohol and paracetamol (women: 6, men: 8). The type of ethanol abuse affects its interaction with acetaminophen toxicity. Many reports suggest that paracetamol hepatotoxicity increases in people who chronically abuse ethyl alcohol. This is due to increased formation of NAPQI, caused by decreased glutathione levels, upregulation of CYP2E1 activity, and increased synthesis of CYP2E1 (a cytochrome P450 enzyme that metabolizes both ethanol and paracetamol). However, acute alcohol abuse reduces the hepatotoxicity of acetaminophen because ethanol is a competitive substrate of CYP2E1, reducing NAPQI production [24, 25, 26].

A major limitation of this study is the lack of clinical data. The patients whose samples were tested were hospitalized in different centers across the province, making it impossible to collect detailed clinical data for all patients. This provides opportunities for future studies, which could also extend to data from other regions of Poland.

CONCLUSIONS

From 2018 to 2022, there was an increase in the number of paracetamol concentration evaluations in patients hospitalized in the Kuyavian-Pomeranian Voivodeship.

1. The highest percentage of patients suspected of paracetamol poisoning were women.
2. Toxic paracetamol concentrations were found more frequently in women than in men.
3. Paracetamol analyses were most often performed on patients aged 3–17.
4. Toxic paracetamol concentrations were most frequently observed in patients aged 3–17.
5. The measured positive paracetamol concentrations were most often within toxic levels.

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