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Exploring the Potential for Paracetamol-Related Drug Interactions in a Hospitalized Elderly Population

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Abstract:

In this research, patients hospitalized to a geriatric medicine department are studied to determine the clinical effect of paracetamol use and the risk of possible drug-drug interactions. Methods. Patients who had been given paracetamol before or during their hospital stay were the subjects of a retrospective and longitudinal research. Documentation of co-occurring drugs, diagnoses, biochemical values, and adverse events during admission was examined in the hospital records of the patients who were part of the study. In order to evaluate the potential clinical effect of the discovered drug-drug interactions, these measures served as a clinical follow-up. Final product. During the research period, a total of 104 patients were hospitalized. With a mean age of 86 years, 91 (87.5%) of these individuals were prescribed or treated with paracetamol. Among these, 10% were deemed to be at high risk of possible paracetamol-drug interactions. Warfarin, valsartan, and phenytoin were all mentioned in connection with seven of the possible drug-drug interactions. Severe clinical events or aberrant biochemical results were experienced by six out of nine individuals who were considered to be at risk. Out of four patients whose INR levels were elevated (range: 3.2-4.6), one was anaemic and one had hematemesis. Two female patients, with ALAT/ASAT levels of 55/42 U/I and 87/51 U/I, respectively, reported elevated levels. One person had high blood pressure. In summary. Paracetamol was prescribed to the vast majority of individuals included in this research. As a result of the possible drug-drug interactions that were found, six individuals were found to have aberrant biochemical results or were suffering clinical occurrences while hospitalized.

Introduction

One of the most diverse and rapidly expanding demographics in our society is the elderly [1, 2]. Arthritis, bone and joint problems, and other chronic diseases are more frequent among the elderly, making pain a regular experience for this population [3]. Paracetamol is the first-line analgesic in Denmark [8] and is used at a maximum dose of four grams per day [9]. It is widely accessible without a prescription and is regularly used for acute and mild to moderate pain [4-7]. It is commonly believed that patients admitted to geriatric medicine departments are more fragile and at a higher risk of adverse events because they are often treated with concomitant medication for associated diseases [11, 12], and clinical trials involving elderly patients are either underrepresented or do not include them [10]. The pharmacokinetics and pharmacodynamics of these drugs vary with age, making these individuals more susceptible [13]. Potential toxicity and drug-drug interactions (DDIs) may become more likely outcomes of this [10, 12]. It has also been shown that the pharmaco-kinetics of paracetamol are significantly affected by age and sex. Especially in older female patients, this causes paracetamol concentrations to rise with age [14]. These results do not warrant the suggestion that the maximum daily dose for older patients be reduced from 4 grams [2, 8, 15].

Multiple investigations have documented and examined pDDIs involving paracetamol and the anticoagulant warfarin [16-21]. The decrease in warfarin clearance [22] and subsequent increase in the international normalized ratio (INR) are anticipated outcomes of this interaction, which is thought to be a pharmacokinetic interaction [19]. Dangerous bleeding might result from this. In a case report from Denmark in 2015, an 83-year-old man with atrial fibrillation and back discomfort passed away due to an untreatable intracerebral hemorrhage, which was one of the fatal DDIs mentioned [23]. An increase in the activity of paracetamol metabolized by CYP1A2 and CYP3A4 may be possible if the activity of CYP2E1 decreases with age [24]. Consequently, it inhibits CYP2C9, which metabolizes S-warfarin, and competes with R-warfarin metabolism. An rise in concentration of the five-times more powerful S-isomer than the R-isomer may occur as a consequence of this [21, 24-26].

1. Aim of the Study

The aim was to investigate the use of paracetamol in elderly patients, who have been hospitalized in a department of geriatric medicine at a secondary hospital providing com- prehensive health services. The focus was to identify the number of patients at risk of pDDIs with paracetamol and to provide a follow-up assessment of the clinical impact hereof by thoroughly investigating the patients' journals.

2. Method

2.1. Settings. The Department of Geriatric Medicine at Bispebjerg Hospital is a department with the capacity of 28 beds and a coverage area of appr. 400,000 citizens in an area that is part of greater Copenhagen and with a very diverse population. The department has a yearly admission of appr. 900 patients per year, whereas appr. 60% is admitted directly from the emergency department. Data for all admitted patients during appr. 5 weeks were collected and reviewed (in the period 1st of September to 10th of October 2016).

2.2. Screening of Patients. All electronic journals of patients aged 65 years or more, hospitalized in the Department of Geriatric Medicine at Bispebjerg and Frederiksberg, were screened for registration of any prescribed or consumed paracetamol upon or during their hospitalization. If para- cetamol was used or prescribed upon or/and during ad- mission, the patient's relevant biochemical values were registered; diagnoses upon and under admission and chronic and temporary diagnoses were identified by reviewing the anamneses and patient files. Also, clinical incidents during hospitalization were registered. These in- cidents were defined as the potential consequences of the DDIs described in the applied DDI databases. The remaining medications were also registered (medication history upon admission, prescriptions during hospitalization, active medication on the day of discharge, and administered medicine during hospitalization). The number of drugs was categorized and registered as the fifth level of ATC, both as needed medication (PRN) and regular prescription.

2.3. Data Management. The percentage of the patients re- ceiving any treatment with paracetamol was calculated, including both the number of regular medications and PRN. For those who did receive any paracetamol treatment, the average administration of paracetamol per day per patient was calculated and compared toward the maximum rec- ommended dosage.

The known pDDIs with paracetamol and *third-line* pDDIs were identified by using the databases *Micromedex* (MM), interaktionsdatabasen (ID), and *pro.medicin* (PM). Only pDDIs classified as *major* and *moderate* severity at MM and *critical* and *potential* problematic at ID were considered for this study.

A *third-line* pDDI was defined as a pDDI including the drug that also causes a pDDI with paracetamol. For instance, simvastatin-warfarin is a *third-line* pDDI because warfarin also can lead to a pDDI with paracetamol. This *third-line* pDDI may influence the pDDI between paracetamol and warfarin. A *third-line* drug was defined as the drug that had a pDDI with the same drug that was

identified to have a pDDI with paracetamol. For instance, simvastatin is the *third-line* drug in the example of *third-line* pDDI. The patients at risk of a pDDI with paracetamol were identified, and subsequently, more thorough assessments of the patients were done. The assessments included an overall medication re- view of the patients' remaining medication.

Eventually, the patients at risk of pDDIs with para- cetamol were evaluated due to any relation between the pDDIs with paracetamol and their biochemical values, di- agnoses on admission or incidents noted in their journal during hospitalization. Incidents were identified according to key words in the applied DDI databases.

3. Results

During the data collection period, 104 patients were ad- mitted to the Department of Geriatric Medicine and their patient files were reviewed. As seen in Table 1, 91 patients (87.5%) received paracetamol upon admission and/or during their hospitalization, of which 55% received it as a regular medication. The patients receiving paracetamol were as a median hospitalized for eight days. The median age was 86 years, and the majority were female (64.8%). The patients received several concomitant medications, with an increase of 28.5% of median prescribed medication from admission to discharge. Nine patients (10%) were identified to be at risk of a pDDI with paracetamol. No patients received more than recommended daily doses, but 26.4% received more than three grams per day as a mean. In addition, more than half of the patients, who received paracetamol as a regular medi- cation at discharge, did receive one or more of other an- algesics as regular medication—with oxycodone as the most frequently used add-on.

The different pDDIs with paracetamol are shown in Table 2, which also illustrates which pDDIs were listed in the three different databases ID, MM, and PM. Seven of the patients were identified at risk of the pDDI with paracetamol and warfarin. One patient was at risk of a pDDI with paracetamol and phenytoin. The last patient was at risk of a pDDI with paracetamol and valsartan.

TABlE 1: Data of the 91 patients receiving paracetamol.

Gender (female/male)	59/32
	Median (range)
Age (years)	86 (68–101)
Duration of hospitalization (days)	8 (1–31)
Number of other drugs upon admission[A,B]	7 (0–19)
Number of drugs at discharge[A]	9 (2–20)
Number of drugs, total exposure[A]	15 (4–29)

[A]Not including paracetamol. [B]Eight patients did not have any registration of their medication history upon admission. The number of drugs upon admission was registered from the medication history described in the patients' journals upon the admission (not necessarily from the Department of Geriatric Medicine). The numbers of drugs at discharge and total ex- posure were registered from EPM and include both regular and PRN medication, and all prescriptions were registered except fluid infusions. The drugs were categorized in ATC codes. EPM – electronic patient module; PRN – as needed; pDDIs – potential drug-drug interactions; ATC – Ana- tomical Therapeutic Chemical Classification System.

TABlE 2: pDDIs described in the three different databases and the number of pDDIs for the 91 patients.

Potential DDI with paracetamol	ID	MM	PRO	Incidents number (%)
Warfarin	+	+	+	7 (7.7%)
Phenytoin	+	+	0	1 (1.1%)
Valsartan	+	0	0	1 (1.1%)
Isoniazid	+	++	0	0
Pneumococcal 13-valent vaccine	0	++	0	0
Imatinib	0	++	0	0
Pixantrone	0	++	0	0
Carbamazepine	0	+	0	0
Acenocoumarol	0	+	0	0
Lixisenatide	0	+	0	0
Zidovudine	0	+	0	0
Busulfan	0	+	0	0
Piperaquine	0	+	0	0
Diflunisal	0	+	0	0
Sulfinpyrazone	0	+	0	0
Aliskiren	+	0	0	0
Phenprocoumon	+	0	0	0

0 – pDDI is not mentioned. + – pDDI is marked as "potential problematic" and "moderate severity" for ID and MM, respectively. ++ – pDDI is marked as "critical" and "major severity" for ID and MM, respectively. PM does not classify DDIs. pDDI – potential drug-drug interaction; ID – interaktionsdatabasen.dk; MM – Micromedex; PM – pro.medicin.dk.

As seen in Table 3, seven of the patients used para- cetamol before admission according to their medication history obtained at admission. One patient did not obtain a medication history. The dose of paracetamol was not specified for another patient, and furthermore, it was not specified for four other patients if the prescription of par- acetamol was as PRN or regular medication. Seven patients were discharged or transferred with an active prescription of paracetamol either as PRN or regular medication or in combination; one patient was paused, and another was discharged without paracetamol.

As seen in Table 4, the range of age of the nine patients at risk was 69 to 95 years, and eight of the patients were female. Six of the patients had a low haemoglobin value, three of them with a value between 5.0 and 6.0 mmol/l (moderate anaemia). Six of the patients had leucocytosis (indication of unspecific inflammation) with the highest value of 17.4 billion leukocytes per litre. Six of the patients had an esti- mated glomerular filtration rate (eGFR) below the reference value (indication of a poor function of the kidneys), two of which had an eGFR below 40 mmol/l. Only two patients had measures of alanine aminotransferase (ALAT) (indication of liver damage). Both patients had a value slightly above the reference with the highest value of 87 U/l. All patients had measures of aspartate aminotransferase (ASAT) (indication of damage to the liver and other tissues as muscles, pancreas, lungs), and the same two patients mentioned above did have a value slightly above the reference value. Five of the patients at risk of a pDDI with paracetamol and warfarin had sub- or supratherapeutic INR. Only one patient had a sub- therapeutic INR of 1.7. The remaining patients had supra- therapeutic values, with the highest value of 4.6. In addition, all the patients at risk of a pDDI with paracetamol had *third- line* pDDIs in the range of one to five other *third-line drugs.* The pDDI of paracetamol and warfarin can lead to bleeding and anaemia, one of the three patients who had moderate anaemia experienced bleeding and hematemesis, during the hospitalization. The pDDI of paracetamol and phenytoin can lead to insufficient effect of paracetamol and an increased risk of hepatotoxicity. The patient at risk of this pDDI had both an episode of pain breakout and as well a suspicion of hepatotoxicity mentioned in her journal. The pDDI of paracetamol and valsartan can lead to tachycardia and hypertension, and the patient at risk had hypertension mentioned in her journal. She was known to have irregular hypertension according to the hospital records.

In the aggregate, four of the nine patients experienced
incidents during their hospitalization that could be related to the pDDIs with paracetamol.

As seen in Table 5, the patients at risk had in average six chronic diagnoses (range, four to nine) and 7 patients were transferred from the emergency department and two from an outpatient clinic.

Four of the patients that experienced increased INR (patients 2, 3, 6, and 7) were either admitted with or di- agnosed during admission with an infection (three with urinary tract infection and one with pneumonia). The pa- tient in risk of pDDI with phenytoin and paracetamol was hypotensive and had malnutrition.

To sum up, six patients had either influenced bio- chemical values (patients 2, 3, 6, and 7) and/or experienced
incidents (patients 3, 5, 7, and 9) during hospitalization that relates to the outcomes described in the applied databases.

4. Discussion

This study shows that most patients hospitalized at a de- partment of geriatric medicine received treatment with paracetamol, not surprisingly, indicating that many elderly patients experience pain. A previous systematic review de- scribed that, in Denmark in 2013, 23% of patients in age group 65–79 years and 45% in age group 80–89 years

TABlE 3: The nine patients at risk of known pDDIs with paracetamol and their consumption of paracetamol.

Patient	Duration of hospitalization (days)	On admission (g)	Total administered g		At discharge (g)		Maximum recommended dose complied
		Regular	g	g/day[D]	Regular	PR	

		PR					N		
		N							
1	7	N/a	N/a	28	4	2	2	Yes	
2	7	0	4	3	0.43	0	4	Yes	
3	9	0	0	1	0.11	0	0	Yes	
4	7	0	4	16	2.29	3	0	Yes	
5	15	4[A]	N/a	50	3.33	0[C]	0	Yes	
6	9	4[A]	N/a	36	4	4	0	Yes	
7	31	4[A]	N/a	91	2.94	4	0	Yes	
8	7	0	+[B]	14	2	3	1	Yes	
9	8	1[A]	N/a	27	3.38	4	0	Yes	

[A]It was not specified if the prescription was as PRN or regular medication. [B]The amount was not specified. [C]The prescription 4 × 1000 mg per day was paused the day of discharge. [D]The mean administration in grams of paracetamol per day during hospitalization. pDDI – potential drug-drug interaction; PRN – as needed; g – gram; N/a – not available.

TABLE 4: For the nine patients at risk, biochemical values, pDDIs with paracetamol, *third-line* pDDIs, and incidents during hospitalization that relates to pDDIs with paracetamol.

Patient case		1	2	3	4	5	6	7	8	9
Gender (F/M)		M	F	F	F	F	F	F	F	F
Age (years)		71	91	86	82	69	95	89	95	87
Biochemistry	Reference value									
Hgb. (mmol/l)	M: 8.3–10.5 or F: 7.3–9.5	—	7.2	5.3	6.9	6.1	—	6.0	—	5.1
Leu. ($x10^9$/l)	3.5–8.8	17.4	—	10.0	10.3	11.5	11.9	13.2	—	5
eGFR (ml/min)	>60	—	43	36	—	—	59	53	41	27
ALAT (U/l)	M: 10–70 or F: 10–45	N/a	N/a	N/a	N/a	55	87	N/a	N/a	N/a
ASAT (U/l)	M: 15–45 or F:15–35	—	—	—	—	42	51	—	—	—
INR	<1, 2, or 2-3[A]	—	3.5	3.8	1.7	—	3.2	4.6	—	—
Potential drug-drug interactions										

pDDI1	Paracetamol and warfarin	+	+	+	+		+	+	+		
pDDI2	Paracetamol and phenytoin					+					
pDDI3	Paracetamol and valsartan										+
Number of *third-line* pDDIs with											
	Warfarin	5	3	2	2		4	5	4		
	Phenytoin					5					
	Valsartan										1
Incidents at or during hospitalization[B]											
pDDI1	Bleeding or anaemia[C]			+				+			+
pDDI2	Pain					+					
	Hepatotoxicity					+					
pDDI3	Tachycardia										
	Hypertension										+

N/a – not available; — – if the value is within the reference value. The biochemical values mentioned are the most abnormal values during the hospitalization in the Department of Geriatric Medicine. Reference values are according to the mentioned value in OPUS. [A]The treatment level during warfarin treatment with the indication of atrial fibrillation (given by sundhed.dk). [B]The patient's diagnose upon admission or did the patient experience any incidents during hospitalization that could relate to the pDDI with paracetamol (according to the outcomes described in the applied databases). [C]Anaemia is defined as haemoglobin 6.0 or less. pDDI – potential drug-drug interaction; *third-line* pDDIs: pDDIs with the same drug that is identified to have a pDDI with paracetamol; F – female; M – male; Hgb – haemoglobin; Leu – leucocytes; eGFR – estimated glomerular filtration rate; ALAT –alanine aminotransferase; ASAT –aspartate aminotransferase; INR – international normalized ratio; U – unit.received prescribed paracetamol [27]. This indicates that patients in a department of geriatric medicine suffer from more pain than elderly in the remaining society. As several (26.4%) received more than three grams of paracetamol per day as a mean, it suggests that several elderly patients receive chronic pain treatment with paracetamol. The aforemen- tioned review concluded that paracetamol as a chronic pain treatment showed minor efficacy and doubtful clinical

Furthermore, the patient's *third-line drugs* and their dosage regime might be able to influence the outcome of the in- teraction between paracetamol and warfarin. Also, in- fections are thought to increase the risk of supratherapeutic INR with or without antibiotic exposure, but to our knowledge, this is only showed in a study that investigate patients receiving warfarin and who develop an acute upper respiratory tract infection [31]. The underlying mechanism is unknown, and the potential explanations mentioned in the article include reduced oral intake and decreased con- sumption of vitamin K-rich foods, the effect of paracetamol- containing cough and cold remedies that can increase the INR, or increased clotting factor catabolism associated with fever [31]. All in all, explanations not necessarily have anything to do with the general perception of an infection. Despite no serious outcomes like severe bleeding or death, four of the investigated patients developed abnormal biochemical values or clinical incidents that could be caused by this well-documented DDI with warfarin and para- cetamol. The heterogeneity of elderly patients can explain why some are more prone to this DDI than others. Patients who are *poor metabolizers* of the CYP2C9 will also have decreased clearance of warfarin, as the more potent *S*-isomer of warfarin is metabolised by this enzyme [26] and be more prone to this DDI. Due to this heterogeneity and various outcomes for patients in concomitant treatment with par- acetamol and warfarin, a previous study recommended that more serious safety consideration should be given for pa- tients at risk of this interaction [20]. The patient at risk of a pDDI with paracetamol and phenytoin experienced clinical incidents of both pain and decreased liver function. This patient was also identified as malnourished, and the de- creased liver function was assessed to be associated with poor nutrition by the hospital physician. Phenytoin induces glucuronidation [32], as well as oxidation by inducing CYP3A4, which may lead to decreased area under the curve of paracetamol, due to an enhancement of first-pass metabolism of paracetamol [33]. This can lead to decreased analgesic effect. Theoretically, the induction of CYP3A4 increases the formation of NAPQI. This can increase the risk of hepatotoxicity due to a potential depletion of glutathione storage for further conjugation of NAPQI. This is to our knowledge only shown in patients who have taken anoverdose of paracetamol, hence depleting glutathione storage [34–38]. Due to the patient's malnourishment and inflammation, she was likely to be at risk of depletion of glutathione storage [39]. In combination with her high daily dosage of paracetamol and regular dosage of phenytoin, it is likely that her incidents were related to the pDDI.

The last patient at risk of a pDDI was the patient re- ceiving valsartan. During hospitalization, the patient expe- rienced hypertension. A previous study showed a significant increase in blood pressure in patients treated concomitantly with paracetamol and valsartan, but the mechanism of the hypertensive effect is not fully understood [40]. The patient had a history of uncontrollable hypertension, which may be ascribable to the DDI or other unknown causative factors. The participants in the aforementioned study were ad- ministered one gram of paracetamol twice daily. They were excluded or withdrawn from the study if they were above 65 years of age and had uncontrolled hypertension. The patient in our study then seemed to be at a much higher risk of this pDDI because of her higher age, possible altered pharma- cology, and uncontrollable hypertension. Particularly, this is because of the increased prescription dosage of paracetamol during hospitalization. This indicates that the healthcare providers had not identified or suspected the pDDI or assessed it as clinically relevant.

The knowledge of the widely used paracetamol's po-
tential to interact with other drugs appears to be limited as none of the healthcare providers seemed to suspect the incidents to be related to the pDDIs with paracetamol, which might have been the case.

The finding and objective of our study was not to evaluate if the patients should have reduced or withdrawn their paracetamol treatment. Paracetamol is still the first- line analgesic even in patients at risk of pDDIs [18, 41]. In geriatric patients, untreated pain can have negative out- comes such as decreased quality of life and associated health issues like depression, anxiety, and sleep distur- bances [3]. Thus, the intention of this study was to show that even though paracetamol is considered the safest choice, these pDDIs are important to keep in mind both for physicians, who prescribe it, and the pharmacy, who de- livers it over-the-counter to the patients. The intention is also to make the prescriber think twice when prescribing the drug, a suggestion could be to monitor the effect after a suitable time of treatment, and potentially deprescribe the well-intended treatment in case of DDI findings, other adverse effects, or lack of effect.

A challenge is also when patients purchase paracetamol over-the-counter in ordinary shops. Due to free trade and a lack of required information, patients can encounter po- tentially dangerous situations with the drug.

The strength of this study is that several parameters have been investigated to assess patients at risk of a DDI with paracetamol. It was not only the patients' prescribed medications that were analysed, but also the administration of medication, the incidents during hospitalization, and relevant biochemical values were collected and analysed. These parameters were used as a clinical follow-up, pro- viding a clinical probability impact of the identified DDIs.The limitations were, as for all retrospective studies, the missing possibility to investigate relevant questions to the patients' medication and diagnoses and uncertainty or errors in information from the hospital's files. This study was made on a small number of patients, and a more extensive study is needed to support and empower our findings. This study was an exploratory study investigating the need and feasibility for a greater study to be conducted in the elderly patients consuming paracetamol.

5. Conclusion

Paracetamol was prescribed to the vast majority of patients admitted to the geriatric medicine department of a big metropolitan secondary hospital. Warfarin was the most common medicine to interact with paracetamol, putting patients at risk of significant clinical incidents; over 10% of patients treated with paracetamol were at risk of pDDIs with paracetamol. Although no major complications occurred in any of the patients, this finding does point to the possibility of heterogeneity and confounding variables such as other illnesses, inflammation, metabolism, malnutrition, third-line pDDIs, concurrent medication, and other medical conditions. It was determined that six individuals had biochemical values or hospital incidents that may have been associated with the pDDIs. This study emphasizes the significance of thoroughly evaluating the utilization of paracetamol in susceptible patient populations, always exploring non-pharmacological treatment options prior to initiating chronic and long-term medication regimens. Alternatively, in the event that long-term medication does not yield the desired results, it may be prudent to deprescribe the drug in order to prevent severe adverse reactions caused by drug interactions, unnecessary polypharmacy, and illogical medical interventions.

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