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Case Report

Secondary Acute Pancreatitis Associated with Paracetamol and Codeine Administration after Dental Treatment: Literature Analysis and Clinical Case Study

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Abstract

Objectives: To review current literature to identify possible secondary complications in response to the administration of paracetamol and codeine as analgesics in the field of dental treatment, and the discussion of a case of secondary acute pancreatitis triggered by the administration of both of these active ingredients.

Materials and Methods: A 28-year-old patient, not exhibiting any pancreatic or hepatobiliary condition, was diagnosed with acute pancreatitis 3 h after taking a 500-mg dose of paracetamol and a 30-mg dose of codeine prescribed as a pain-relief therapy after the extraction of tooth #4.8 (right-lower third molar).

Outcome and Discussion: Acute pancreatitis is an acute inflammatory condition affecting the exocrine cells in the pancreas, in which secretions from the pancreas and/or its components

may flow into the peritoneal cavity and the bloodstream, resulting in serious local and systemic consequences. Therefore, acute pancreatitis is an event characterized by an unpredictable course and constitutes a real medical emergency. In most of the patients with acute pancreatitis, the condition resolves spontaneously, generally within 3–7 days from the beginning of pharmacological therapy.

Conclusions: Although paracetamol and codeine possess pain-relieving properties with a high therapeutic index, it is essential to perform an adequate preliminary medical history evaluation, which would inform the patient of the possible adverse reactions, whether allergic or idiosyncratic in nature, following the use of drugs taken for the first time or taken sporadically.

Keywords

Pancreatitis; analgesics; paracetamol; codeine; complications; dental field

1. Introduction

Acute pancreatitis is an acute inflammatory condition affecting the exocrine cells in the pancreas. It is one of the most common disorders affecting the gastrointestinal tract, with an annual incidence ranging from 10 to 20 cases per 100,000 individuals [1, 2]. Acute pancreatitis results in a process of self-digestion of pancreatic parenchyma, induced by premature activation of the enzymes secreted by acinar cells, which are generally activated at the level of small intestine as a result of contact with the enterokinases and the fundamental constituents of nutrition (i.e., proteins, lipids, and carbohydrates) [2].

Clinically, acute pancreatitis manifests with pain symptoms primarily located at the level of upper abdominal quadrants. In addition, frequent local and systemic repercussions occur at the gastrointestinal, biliary, respiratory, cardiac, and renal levels [3]. Serious systemic complications, such as hemorrhagic or vasoparalytic shock, as well as severe metabolic and hemocoagulation disorders associated with acute pancreatitis, with mortality rates of 0%–1% in moderate cases and 15%–30% in severe cases (20% of the total cases), have been extensively described in the literature [1, 2, 4].

Although biliary tract infections, alcohol abuse, metabolic imbalances, and endocrine disorders have been identified as the main causes of acute non-idiopathic pancreatitis, this disease has also been diagnosed in the cases receiving treatment with multiple pharmacological agents, including opiates, high-dose corticosteroids, and paracetamol [5–8].

The aim of the present report was to examine the possible onset of secondary acute pancreatitis after the intake of a common medicinal combination of paracetamol and codeine for pain relief. In particular, the present report analyzed a clinical case of acute pancreatitis induced by the intake of a single dose of paracetamol (500 mg) plus codeine (30 mg) prescribed for pain relief following the extraction of the impacted tooth #4.8 (right-lower third molar).

The analysis of the above-stated case allowed the description of the major complications associated with the use of the combination of paracetamol and codeine in the field of dental care, in addition to the diagnostic, therapeutic, and prognostic issues associated with acute pancreatitis.

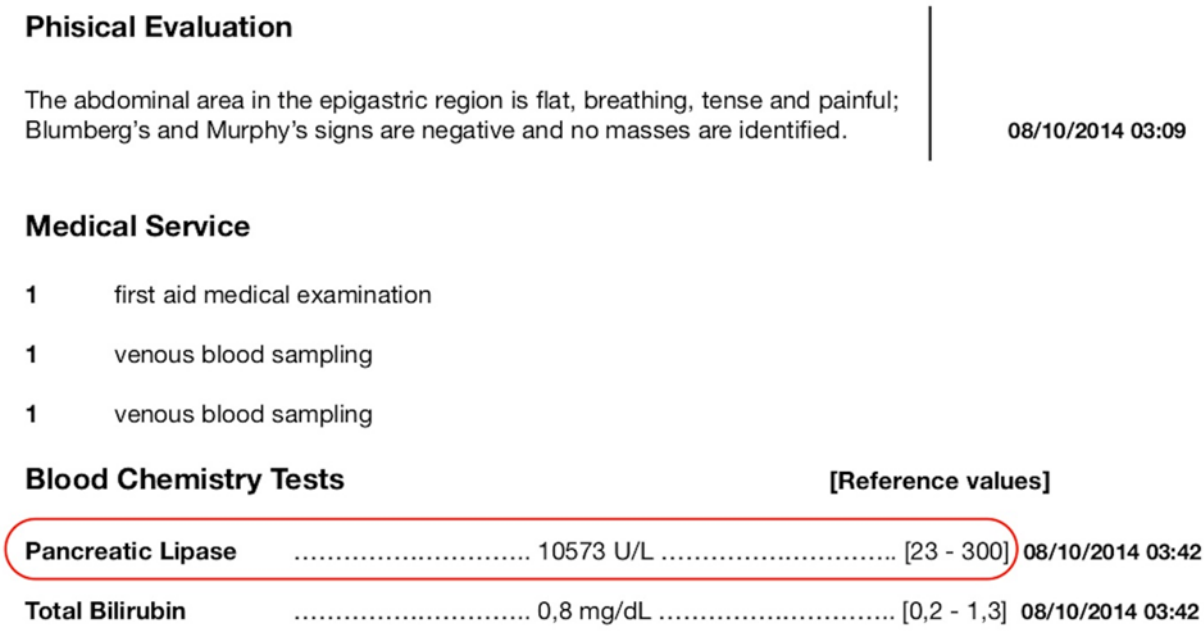
2. Clinical Case

A 28-year-old patient with a near-negative medical history of systemic disorders and with no known allergies arrived at the Oral Surgery Unit of the Dental Clinic, San Paolo Hospital, Milan, for the extraction of the impacted tooth #4.8, which had adversely affected the distal surface of the tooth #4.7 (second lower-right molar). At the end of the surgical procedure, the patient was prescribed analgesics, specifically paracetamol (500 mg) + codeine (30 mg), 1 sachet, to be taken as required, for a maximum of 3 times per day. The patient had never taken either paracetamol or codeine previously and took just one sachet of the prescribed painkiller after dinner (9.00 pm) to alleviate moderate post-operative pain. Three hours later, the patient began experiencing strong abdominal pain accompanied by exhaustion and fatigue, following which the patient along with a family member reported to the Emergency Department of the San Paolo Hospital, Milan.

At the hospital, the patient underwent physical evaluation; at deep palpation, the abdominal area in the epigastric region was flat, breathing was tense and painful, Blumberg's and Murphy's signs were negative, and no masses were identified. Targeted blood chemistry tests (Figure 1) revealed a significant increase in the levels of pancreatic lipase (10,573 U/L), which exceeded the standard threshold values (23–300 U/L) by a great margin, a clinical and diagnostic scenario consistent with iatrogenic acute pancreatitis.

The patient was then urgently admitted to the hospital to further conduct diagnostic tests (abdomen radiography without a contrast agent and ultrasound of the upper abdomen), which did not reveal any focal lesions in the liver, gall bladder stones, or biliary tract dilations. Seven hours post-admission to the hospital, a second abdominal ultrasound was performed which was negative and the abdomen was neither tender nor painful. Therefore, the patient was discharged with a diagnosis of pancreatic insult conceivably induced by pharmaceuticals, and was also provided with post-discharge instructions. Twelve days after the discharge, additional blood tests were conducted, which revealed that the levels of pancreatic lipase had reached within the limits of the standard thresholds (Figure 2).

In regard to the dental procedure, the patient reported no postoperative complications or discomfort and at the time of suture removal, the healing observed was compatible with a normal post-operative course.



Phisical Evaluation

The abdominal area in the epigastric region is flat, breathing, tense and painful; Blumberg's and Murphy's signs are negative and no masses are identified. **08/10/2014 03:09**

Medical Service

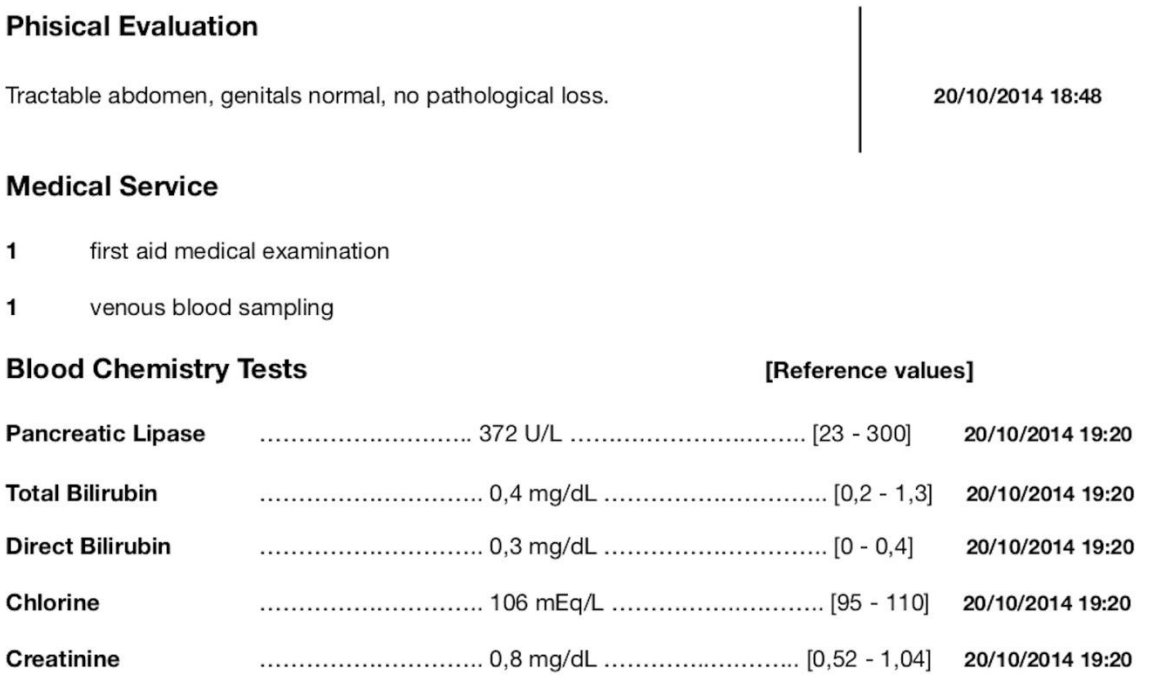
1 first aid medical examination

1 venous blood sampling

1 venous blood sampling

Blood Chemistry Tests		**[Reference values]**	
Pancreatic Lipase	10573 U/L	[23 - 300]	**08/10/2014 03:42**
Total Bilirubin	0,8 mg/dL	[0,2 - 1,3]	**08/10/2014 03:42**

Figure 1



Phisical Evaluation

Tractable abdomen, genitals normal, no pathological loss. **20/10/2014 18:48**

Medical Service

1 first aid medical examination

1 venous blood sampling

Blood Chemistry Tests		**[Reference values]**	
Pancreatic Lipase	372 U/L	[23 - 300]	**20/10/2014 19:20**
Total Bilirubin	0,4 mg/dL	[0,2 - 1,3]	**20/10/2014 19:20**
Direct Bilirubin	0,3 mg/dL	[0 - 0,4]	**20/10/2014 19:20**
Chlorine	106 mEq/L	[95 - 110]	**20/10/2014 19:20**
Creatinine	0,8 mg/dL	[0,52 - 1,04]	**20/10/2014 19:20**

Figure 2

3. Discussion

3.1 Clinical Picture

Acute pancreatitis is a condition of acute inflammation in the exocrine cells of the pancreas, which is distinguished from other related conditions by a pathogenetic model referred to as the "theory of pancreatic self-digestion", which was first validated approximately a century ago [4]. The primal event of this process consists of premature conversion of trypsinogen into trypsin, leading to the activation of additional pancreatic enzymes (zymogens), rupture of the pancreatic channels, invasion of the interstitium by the enzymatic secretions, and the induction of a continuous inflammatory process that damages the pancreas and/or its surrounding structures [2, 4].

Secretions from the pancreas and/or its components may flow into the peritoneal cavity and the bloodstream, resulting in serious local and systemic consequences, including the following: secondary apoptotic processes resulting from the alterations in the cell membranes (caused by pancreatic phospholipases), alterations in the vascular walls which may in turn induce hemorrhagic events (due to pancreatic elastases), and steatonecrosis of intra- and peri-pancreatic tissues (caused by pancreatic lipases present in bile salts, which flow back to the pancreas through the ducts) [9, 10]. Furthermore, the action of trypsin may cause the induction of the vasoactive peptide system (resulting in vasodilation, increased vascular permeability, and hypovolemia), and lead to significant alterations in the blood coagulation system, particularly in its procoagulant/antifibrinolytic effects. In such cases, a diagnosis of disseminated intravascular coagulopathy (DIC), with the risk of serious bleeding, may be possible [4].

A variable combination of these pathological processes causes acute pancreatitis to be an event that is characterized by an unpredictable course, and therefore, it constitutes a real medical emergency [2]. The major symptom of this disease is the "bar-like" abdominal pain that occurs in the epigastric and peri-umbilical area, extending toward the right hypochondrium, and in rare cases to the left hypochondrium, and which is generally irradiated to the back and chest. This pain manifests with variable intensity, from mild to tolerable to violent, stabbing, and continuous [2]. The pain is usually experienced more intensely in the supine position and is relieved by sitting down with the chest bent forward and the knees bent [11]. This condition may also be accompanied by significant emesis, nausea, and abdominal distension associated with gastrointestinal hypomotility and chemical peritonitis [2, 11]. Vomiting associated with acute pancreatitis differs from the vomiting of gastric origin, in the context that it does not provide any relief to the abdominal pain; and sometimes, it even aggravates the pain [3]. Despite the severity of the abdominal pain, only 30% of the patients develop a defense reaction and muscle contracture following the palpation of the abdomen [3]. Acute pancreatitis has also been commonly associated with meteorism, especially in the epigastrium and hypochondriac areas, while paralytic ileus has been reported to occur in most of the cases [3, 11].

3.2 Diagnosis

Although no laboratory data or pathognomonic clinical signs are available for acute pancreatitis, its accurate diagnosis relies on the evaluation of multiple biological markers and inflammatory mediators which are indicative of pancreatitis and its severity [12]. LeveL^{-1}

instrumental examination should include the following: amylase and lipase levels; CBC with white blood cell differential; metabolic panel including the blood levels of nitrourea, creatinine, glucose, and calcium; triglyceride levels; urinalysis; and arterial blood gas analysis [12].

The most evocative parameters of acute pancreatitis include:

- a marked increase in the amylase levels within 24 h of onset, with the recovery of the normal value of 70–300 IU/L (evaluated using the chromogenic assay) within 3–4 days of occurrence;
- a significant increase in the transaminase and lactic-dehydrogenase levels, proportionate with the extent of pancreatic cellular necrosis;
- a significant increase in the pancreatic lipase concentration. This alteration generally remains for a longer period of time compared to the increase in the amylase levels [3].

Hematocrit may increase following the exudative effusion in the peritoneum, or reduce as a result of bleeding [3]. Among the most suitable instrumental investigations, abdomen radiography without a contrast agent with the patient in a supine and erect position is recommended to exclude other acute abdominal conditions, such as intestinal perforation or acute intestinal obstruction [3].

3.3 Therapy

In most of the patients with acute pancreatitis, the condition resolves spontaneously, generally within 3–7 days from the beginning of the pharmacological therapy with the following:

- analgesics (which are generally non-steroidal anti-inflammatory drugs or NSAIDs);
- intravenous administration of fluids and colloidal solutions aimed to maintain a normal intravascular volume;
- parenteral or enteral nutrition [11].

Although Previously, prophylactic antibiotic therapy was commonly administered to limit the onset of septic complications associated with the persistence of the necrotic tissue, which were responsible for approximately 80% of the deaths due to acute pancreatitis [3]. However, it has been reported that the rate of pancreatic infections does not decrease during antibiotic prophylaxis [11]. Therefore, it is advisable to administer antibiotic therapy only if the clinical or instrumental investigations (blood culture) are consistent with the sepsis in progress [11].

If the systemic medical therapy fails, the next most suitable treatment is surgery, which is the debridement of the necrotic pancreatic tissue combined with the removal of the retroperitoneal exudate, and is performed after pancreatic skeletonization in the abdominal cavity, isolation of the surrounding fatty tissue, and peripancreatic fluid drainage [1].

3.4 Paracetamol

Paracetamol is an analgesic and antipyretic molecule, which exhibits moderate activity on cyclo-oxygenases 1 and 2 (COX–1 and COX–2), and possesses inhibiting properties at the peripheral tissue level, as a result of which, it does not exhibit any anti-inflammatory action. It is generally administered orally, with its pharmacokinetics characterized by good gastric absorption, peak plasma concentration attained within 30–60 min of ingestion, and a half-life of approximately 2–3 h [13].

The aAdministration of a normal dose of paracetamol (not exceeding 4–6 g/day for adults) involves hepatic microsomal metabolism, distributed at 95% in the glucuronation and sulfation pathway (with the production of non-toxic acetaminophen-sulfate and glucuronide metabolites) and 5% in the conjugation pathway with cysteine through an independent pathway mediated by cytochrome P450 [13]. However, with the administration of an overdose of paracetamol, the glucuronidation and sulfation pathway becomes saturated, and as a consequence, the increased amount of paracetamol is metabolized via cytochrome P450 by conjugation with cysteine [13]. However, if this alternate pathway also becomes saturated following the depletion of the cysteine stocks in the liver, an intermediate metabolite N-acetyl-p-benzoquinquinone is released, which is characterized by documented hepatotoxic activity with the possible development of fulminant liver insufficiency (FLI). This is potentially lethal in the cases of administrations equal to or greater than 15 g of paracetamol [13, 14].

In the event of overdose intoxication, immediate administration (ideally within 8–10 h) of N-acetylcysteine allows rapid restoration of the hepatic reserves of cysteine by supplying the cytochrome P450 substrate necessary for the metabolism of paracetamol [13]. Multiple authors have reported that even though the adverse reactions in response to paracetamol intake manifest primarily through secondary liver toxicity resulting from the overdose, this condition could be, although rarely, correlated with the following:

- cardiotoxicity associated with non-specific ECG alterations (which primarily affect the ST segment and the T wave of the ECG), consistent with pericarditis;
- lung damage associated with parenchymal lesions or pulmonary circulation disorders;
- blood toxicity associated with thrombocytopenia (which is a common finding in all forms of liver failure), responsible for Henoch–Schönlein purpura (HSP) and gastrointestinal bleeding in extremely severe cases;
- esophageal varices and ascites associated with liver failure;
- metabolic alterations, such as acidosis, hypo/hyperglycemia, etc., associated with liver failure;
- secondary kidney failure occurring as a result of acute tubular necrosis, interstitial nephritis, or damage to the distal tubule. It may occur simultaneously with liver failure or rarely without liver damage;
- the onset of hyperamylasemia, which at a low frequency may lead to acute pancreatitis [7, 8, 13–16].

The study conducted by Schmidt et al. [14] with 814 patients suffering from paracetamol poisoning demonstrated the onset of acute pancreatitis only in 33 cases (4% of the total cases, 14% of the cases with hyperamylasemia associated with paracetamol overdose). In 18 of these 33 cases, acute pancreatitis was observed to be complicated by fulminant liver failure. The overdose values used in this study ranged between 18 g and 50 g.

et al. [16] reported the case of a patient who experienced abdominal pain and hyperamylasemia together with acute pancreatitis, for three times after paracetamol overdose, which was confirmed through a computed tomography-based evaluation.

However, the authors of this paper were not aware of the reports on the association of acute pancreatitis with the administration of normal doses of paracetamol.

3.5 Codeine

Codeine is a low-medium-efficacy opiate derivative belonging to the phenanthrene family, which acts as a partial agonist of opiate receptors μ, δ, and K, providing analgesic efficacy much lower in comparison to morphine [13]. Administration of 30–60 mg of codeine (up to a maximum dose of 240 mg/day, divided into 4 administrations at 4-h intervals) is generally adequate for the control of post-operative pain arising as a result of minimally invasive surgical procedures [17], such as oral surgery. The efficacy of an analgesic is subject to inter-individual variability, which is related to the genetically predetermined efficiency of the CYP2D6 microsomal pathway, which is used for the conversion of codeine into its active metabolite morphine [17, 18]. In particular, the analysis of the CYP2D6 genotype coding allowed the distinction among the corresponding four different phenotypes in relation to the conversion efficacy; the four phenotypes are as follows:

- poor metabolizer (PM);
- intermediate metabolizer (IM);
- extensive metabolizer (EM);
- ultra-rapid metabolizer (UM).

The PM subjects are not much sensitive to the analgesic efficacy of the opiate derivatives, while the UM subjects develop an extremely effective response. Similarly, in case of an overdose, the PM subjects are less susceptible to the side effects associated with morphine poisoning, while the UM subjects have a significantly higher risk of developing adverse effects, such as respiratory depression, gastrointestinal bleeding, addiction, and acute pancreatitis [18, 19].

Administration may be individual or in combination with paracetamol or other NSAIDs. Multiple authors have confirmed that a combination of different analgesic subjects facilitates the control of acute postoperative pain and that the combination of paracetamol and codeine is particularly effective in this regard [13, 17]. However, there is no evidence that the combination of multiple analgesics promotes effective pain management [17]. The onset of acute pancreatitis following the administration of therapeutic doses of codeine, combined or not with paracetamol, has also been reported by various authors [19, 20].

Hastier et al. [19] described the clinical cases of four patients, three women and one man (average age: 50.2 years), who presented clinical, biochemical, and radiological evidence of acute pancreatitis following the intake of codeine at therapeutic doses (40–60 mg). In one of the cases that were analyzed by these authors, codeine was used in combination with paracetamol. In the described cases, the onset of intense abdominal pain occurred within 3 h of drug intake. In three of the four cases, involuntary intake of the active ingredient led to the exacerbation of the clinical scenario. All the patients who underwent ultrasound evaluation had previously undergone a cholecystectomy more than five years earlier.

Moreno Escobosa et al. [20] reported the case of a 42-year-old male patient who experienced epigastric pain in association with marked hyperamylasemia after the intake of one amoxicillin/clavulanate tablet (500/125 mg) and one paracetamol/codeine (500/30 mg) prescribed for a respiratory infection. The onset of pain in the epigastric region occurred approximately an hour after the intake of paracetamol and codeine, and the patient's medical history revealed that he had undergone a cholecystectomy five years ago. Both the authors [19, 20] supported a pathogenetic hypothesis which assumes that codeine induced a spasm which in turn affected the sphincter of Oddi, as already demonstrated by Hastier et al. in 1997, following the subcutaneous

codeine and morphine injections at therapeutic doses. The spasm occurred within 5 min of administration and lasted for at least 2 h [19]. Despite this evidence, there have been no reports so far demonstrating acute pancreatitis being solely related to the sphincter spasm induced by codeine intake [20]. Therefore, the authors [19, 20] suggested that codeine intake primarily constitutes a precipitating factor for the onset of acute pancreatitis, in the presence of a pre-existing dysfunction of the sphincter of Oddi, which was observed to be correlated to gallstones in 905 cases. In this context, a cholecystectomy may constitute a risk factor for the development of acute pancreatitis following the use of codeine. In fact, greater than 60% of the patients who underwent a cholecystectomy were diagnosed with abnormalities in the function of the sphincter of Oddi, which could have been a result of the following:

- fibrosis and/or hyperplasia of the smooth muscle of the sphincter;
- stenosis and/or spasm;
- increase in the secondary sphincter pressure due to the reduced storage capacity of the biliary tract.

Tanaka et al. also reported that in patients undergoing gall bladder removal, intrabiliary pressure could be increased through the intravenous administration of morphine [20]. Therefore, it is probable that the onset of acute pancreatitis in the patients undergoing a cholecystectomy and taking codeine might be a result of the combined effect of the codeine-induced spasms at the sphincter of Oddi and the reduced biliary storage capacity due to lack of physiological reserve otherwise offered by the gall bladder [19, 20].

the present report demonstrated that the onset of acute pancreatitis following the use of codeine may occur, although rarely, even in the patients who did not undergo a cholecystectomy and had no history of any biliary tract disease. In agreement with the conclusions formulated by Escobosa et al. [20] in their study, the authors of the present report also believe that acute pancreatitis should be considered a possible side effect of the intake of codeine, especially in the patients who have undergone a cholecystectomy.

4. Conclusion

The clinical case discussed in the present report emphasized that despite the high therapeutic index described in the literature concerning the prescription of paracetamol and codeine as painkillers in the field of dental care, it is essential to perform adequate preliminary medical history evaluation, as well as inform the patient regarding the possible adverse allergic or idiosyncratic reactions following the intake of drugs taken either for the first time or sporadically. In this context, the authors of the present report indicated that paracetamol- and/or codeine-induced iatrogenic pancreatitis could occur in any patient even if no specific condition affects the patient's pancreatic and hepatobiliary areas. In particular, this complication appears to develop more frequently with the use of codeine by the patients who have previously undergone a cholecystectomy.

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Luigi Tagliatesta: Contributed data or analysis tools;
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Competing Interests

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