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PRIKAZ SLUČAJA
CASE REPORT

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Diskoloracije i erozije zuba kao posljedica ovisnosti o kombiniranom analgetiku

Dental Discoloration and Erosion Resulting from Addiction to Compound Analgesics

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Sažetak
Dentalna erozija danas je najčešća nekarijesna promjena na zubima, a nastaje zbog dugotrajnog djelovanja kiselih kemijskih čimbenika na površinu zuba, bez utjecaja bakterija. Ti se čimbenici dijele na unutarnje i vanjske. Unutarnji čimbenik je kiseli želučani sadržaj koji se zbog povraćanja može naći u usnoj šupljini, a vanjske čimbenike predstavljaju sve kisele tvari koje se unose u usta, najčešće pojedine vrste hrane i pića te lijekovi. Svrha ovog prikaza je upozoriti na mogući utjecaj kombiniranog lijeka s analgetičkim učinkom (aktivne komponente – paracetamol, propifenazon, kodein-fosfat i kofein) na promjene na zubima. U radu se opisuju vrlo specifične erozije na usnenim dijelovima zuba te njihova ljubičasto-plavkasta boja uočena tijekom obdukcije pothranjenog 35-godišnjeg muškarca koji je umro tijekom prijma na bolničko liječenje. Heteroanamnestički je dobiven podatak o dugogodišnjoj ovisnosti o kombiniranom analgetiku. Osim promjena na zubima, obdukcijom su ustanovljene erozije sluznice želuca, kronični vrijed u području dvanaesnika, kronična upala jetara te hipoplazija koštane srži. Uzrok smrti bila je obostrana gnojna upala pluća s velikim gangrenoznim žarištem lijevog pluća. Kemijskotoksikološkom analizom potvrđena je prisutnost svih farmakološki aktivnih tvari u mokraći, žučnoj tekućini, tkivu jetara i bubrega, želučanom sadržaju, te u ekstraktu zuba. Raspravlja se o vjerojatnom mehanizmu nastanka promjena na zubima i promjenama na drugim tkivima i organima, kao posljedicama dugotrajne ovisnosti o kombiniranom analgetiku. Ističe se važnost zuba kao prikladnoga za toksikološku analizu metodom plinske kromatografije te važnost interdiciplinarnog pristupa u rješavanju forenzičnih slučajeva. Posebno se ističe izolacija analgetika iz zuba, kao korisna dijagnostička metoda u slučaju sumnje na zloporabu tih lijekova.

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Uvod

Zubni karijes i nekarijesne lezije tvrdih zubnih tkiva najčešće su bolesti zuba (1). Osim dentalne erozije, danas najčešće nekarijesne lezije zbog dugotrajnog djelovanja kiselih (pH<7) kemijskih čimbenika na površinu zuba bez utjecaja bakterija (2,3), na istrošenost zuba utječu i mehanički čimbenici poput abfrakcije, abrazije i atricije. Kiseli kemijski čimbenici koji potiču dentalnu eroziju mogu se podijeliti na unutarnje i vanjske (1–3).

Unutarnji kemijski čimbenik je kiseli želučani sadržaj koji se zbog povraćanja može naći u usnoj šupljini, što je obično povezano s poremećajem u prehrani (bulimijom, alkoholizmom) ili gastroezofagealnim refluksom (1–7).

Vanjske čimbenike predstavljaju sve kisele tvari koje se unose u usta, ponajprije pojedine vrste hrane i pića (agrumi, pića s kolom, vina i pjenušci) te lijekovi (1–3, 8–10).

Introduction

Today, dental caries and non-carious lesions of dental hard tissues are the most common diseases of the teeth (1). In addition to dental erosion, which is the most common non-carious change resulting from long-term effects of acidic chemical (pH<7) factors on the tooth surface without the intervention of bacteria (2, 3), tooth wear is also influenced by mechanical factors, such as: abfraction, abrasion and attrition. Acidic chemical factors causing dental erosion can be divided into intrinsic and extrinsic factors (1-3).

The intrinsic chemical factors include acidic gastric contents reaching the oral cavity as a result of vomiting usually associated with an eating disorder (bulimia, alcoholism) or gastro-esophageal reflux (1-7).

The extrinsic factors include all acidic substances taken into the mouth, primarily certain types of foods and beverag-

U radu je opisan slučaj osobe koja je za života bila ovisna o kombiniranom lijeku s analgetičkim učinkom (sadržaj jedne tablete: paracetamol, propifenazon, kodein-fosfat i kofein). Klinički nalaz u usnoj šupljini upućuje na vrlo izražene dentalne erozije gornjih usnenih ploha sjekutića i očnjaka, uz promjenu boje zuba u ljubičasto-plavkastu. Ovaj prikaz upućuje na to da je specifična i dugotrajna primjena lijeka najvjerojatniji uzrok opisanih promjena na zubima. Također je opisan proces izolacije analgetika iz zuba, što je prema našim spoznajama prvi takav slučaj opisan u literaturi.

Opis slučaja

Mrtvo tijelo muškarca u dobi od 35 godina prevezeno je u Zavod za sudsku medicinu i kriminalistiku radi obdukcije.

U priloženoj medicinskoj dokumentaciji navedeno je da je pacijent umro nakon što je primljen na bolničko liječenje. Bio je dovezen vozilom hitne pomoći. Anamnestički podaci pokazuju ovisnost o Plivadonu®, navodno od djetinjstva, a dnevno je trošio i do četiri pakiranja tableta (40 komada). Povremeno je bio liječen psihijatrijski i uzimao je antidepresive. Prema riječima članova obitelji, posljednjih mjeseci gotovo nije jeo niti pio, bio je nepokretan i slabo je komunicirao. Osim tih heteroanamnestičkih podataka, nije bilo ostale medicinske dokumentacije.

U povijesti bolesti opisuje se kao izrazito pothranjen. Kod pregleda je bio bez svijesti, površno je i plitko disao, a koža i vidljive sluznice bile su blijedožute. Auskulatorno čuli su se hropci i plitko disanje. Akcija srca bila je jedva čujna, a krvni tlak nemjerljiv. Umro je unatoč reanimaciji.

Obdukcijski nalaz

Vanjskim pregledom mrtvog tijela ustanovljena je izrazita pothranjenost – kaheksija (slika 1.) i zaležajni vrijed – dekubitus u predjelu križa. Unutarnjim pregledom uočene su erozije sluznice želuca i kronični vrijed u području dvanaesnika. Osim toga pronađena je obostrana gnojna upala pluća s velikim gangrenoznim žarištem u gornjem režnju lijevoga plućnog krila, što je i bio neposredni uzrok smrti.

Pregledom usne šupljine stomatolog je ustanovio dentalne erozije jakog stupnja (stupanj 3. „BEWE“) vidljive na gornjim sjekutićima i gornjem lijevom očnjaku /12, 11, 21, 22, 23/. Zahvaćale su usnene plohe od vratnog dijela zuba do griznog ruba, uz eksponiranost pulpnih komorica, što je bilo osobito uočljivo na gornjem lijevom središnjem sjekutiću. Zaostali dijelovi dentina na erodiranim zubima bili su diskolorirani, specifične ljubičasto-plavkaste boje (slika 2). Tijekom obdukcijskog pregleda usne šupljine uočena je loša oralna higijena usne šupljine te mnogobrojni karijesi na vratnim dijelovima zuba i nakupine dentobakterijskog plaka.

es (consumption of citrus fruits, cola soft drinks, wines and sparkling wines), and some medicines (1- 3, 8-10).

This paper reports on a case of a lifetime dependence on a compound medication with analgesic effect (ingredients in one tablet include: paracetamol, propyphenazone, codeine phosphate and caffeine). Clinical findings in the oral cavity show pronounced dental erosion of the labial surface of the upper incisors and canine teeth with the teeth having changed color to purple-bluish. This report points to the fact that a specific and long-term application of the medication was most probably the cause of the described changes in the teeth.

It also describes the isolation of analgesic drug from the teeth, which is – to our best knowledge – the first case of such kind described in the literature.

Case Report

Dead body of a man aged 35 was referred for autopsy to the Department of Forensic Medicine and Criminology.

The enclosed medical records indicate that the patient died during hospital admission to receive treatment. The patient was taken to the health care facility by ambulance. The medical history shows a history of addiction to Plivadon®, allegedly present since childhood, stating that the man was taking up to four tablet packages (40 pieces) daily. He received occasional psychiatric treatment, and used antidepressants. According to testimony provided by his family members, for the last few months of life he consumed almost no food and drink, was immobile and barely communicable. Besides the information given by family, no medical records concerning previous diseases were available.

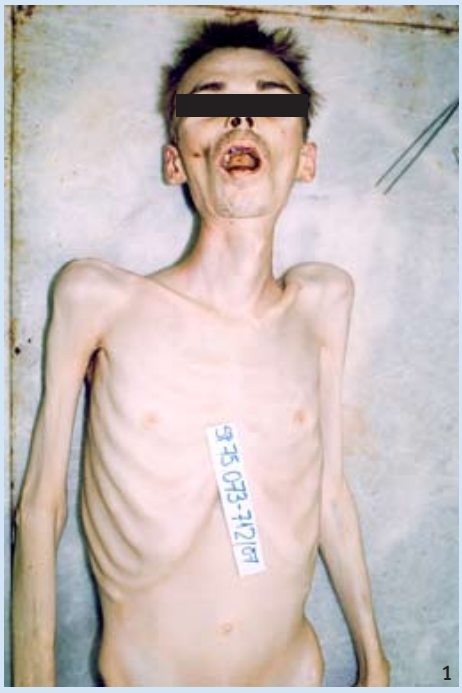
The medical history describes the man as severely malnourished. At examination he was unconscious, had superficial and shallow breathing, and the skin and visible mucous membranes were pale yellow in appearance. On auscultation, rattling sounds and shallow breathing were heard. The heart action was barely audible, and blood pressure immeasurable. Despite resuscitation efforts, a fatal outcome occurred.

Autopsy Report

The external examination of the dead body revealed severe malnutrition – cachexia (Figure 1) and a bedsore – decubitus ulcer in the lower back region. The dental status was very unusual. Type and extent of dental changes called for the assistance of an experienced forensic odontologist who performed further examination. The internal examination showed erosions of the gastric mucosa and a chronic duodenal ulcer. In addition, bilateral purulent inflammation of the lungs with an extensive gangrenous focus in the upper lobe of the left lung was detected and determined as the immediate cause of death. At the autopsy of the oral cavity, poor oral hygiene and a great number of caries in cervical parts of the teeth as well as deposits of dentobacterial plaque were observed.

Also, samples were taken for histopathological and chemical toxicology analysis.

The examination of the oral cavity by odontologist revealed severe dental erosions (BEWE score 3) visible on the



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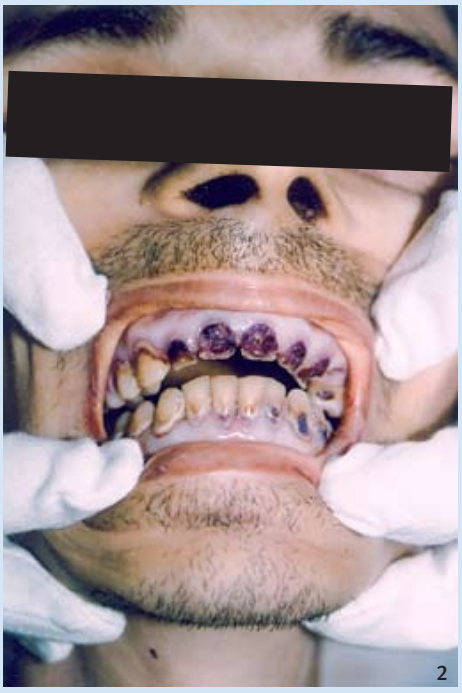

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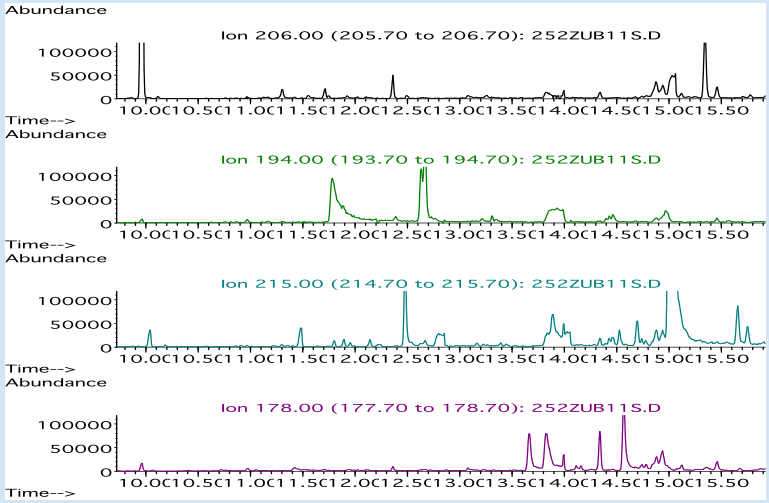
Slika 1. Tijelo pokojnika
Figure 1 General external aspect of the body
Slika 2. Promjene na zubima
Figure 2 Dental changes



Slika 3. Kromatogrami paracetamola, kofeina, propiofenazona i kodeina u zubu
Figure 3 Chromatograms of paracetamol, caffeine, propiophenazone and codeine in tooth extract.

Tijekom obdukcije uzeti su uzorci za patohistološku i kemijsko-toksikološku analizu.

Patohistološki nalaz

Patohistološka analiza potvrdila je gangrenoznu, apscedirajuću upalu pluća, a ustanovljena je i kronična upala jetara te hipoplazija koštane srži.

Kemijskotoksikološki nalaz

Metodom ekstrakcije na koloni punjenoj smolom XAD-2 obrađeni su uzorci krvi, mokraće, žučne tekućine, tkivo jetara i tkivo bubrega. Tako priređeni ekstrakti analizirani su na plinskom kromatografu s masenim detektorom te je utvrđeno:

upper incisors and left upper canine (12, 11, 21, 22, 23). The erosions involved the labial surface of the tooth neck up to the biting edge with exposed pulp chambers that were especially visible on the upper left central incisor. The remaining dentin portions of the eroded teeth showed a specific purple-bluish discoloration (Figure 2).

Histopathological Report

Histopathology confirmed the presence of a gangrenous, abscessing pneumonia, and also revealed chronic liver inflammation and bone marrow hypoplasia.

Chemical Toxicology Report

Samples of blood, urine, bile fluid, liver and kidney tissues were processed using the method of extraction on a column filled with XAD-2 resin. The extracts thus prepared were analyzed by a gas chromatograph coupled to a mass detector to determine as follows:

- u krvi 0,66 mg% propifenazona, 1,50 mg% kofeina te kodein u tragovima;
- u mokraći 0,11 mg% propifenazona, 1,50 mg% kofeina, 0,26 mg% kodeina i paracetamol u tragovima;
- u žučnoj tekućini 1,03 mg% propifenazona, 1,24 mg% kofeina, 0,06 mg% kodeina i paracetamol u tragovima;
- u tkivu jetara i bubrega identificirani su propifenazon, kofein, kodein i paracetamol.

Uzorak kose i želučanog sadržaja ekstrahiran je organskim otapalom, zatim su dobiveni ekstrakti analizirani na plinskom kromatografu s masenim detektorom te je utvrđeno:

- kosa sadržava propifenazon i kodein u tragovima;
- želučani sadržaj sadržava propifenazon, kofein, kodein i paracetamol.

Kvantitativno utvrđene koncentracije djelatnih tvari kombiniranog lijeka nalazile su se u području terapijskih koncentracija.

Zub (gornji lijevi očnjak /23/) mase 0,86 grama mljeven je jednu minutu u mlinu MM 301 (Retsch, GmbH&Co., Haan, Njemačka). Dobiveni materijal ekstrahiran je s 5 mL metilnog alkohola, centrifugiran i filtriran preko filtarskog papira plava vrpca (Munktell 90 mm/391). Ostatak je ekstrahiran s 5 mL etilacetata, te također centrifugiran i filtriran preko filtarskog plavog papira u istu posudu s prvim ekstraktom. Dobiveni ekstrakt otparen je na mali volumen i bio je plavkaste boje. Zatim je siliran s 30 µL BSTFA+1%TMCS 30 minuta na 70°C. Taj je postupak u skladu s onim kojim su se Pellegrini i suradnici koristili pri ekstrakciji opijata i kokaina iz ljudskih zuba (11).

Plinskom kromatografijom s masenim detektorom u siliranom ekstraktu zuba dokazana je prisutnost propifenazona, paracetamola, kofeina i kodeina – farmakološki aktivnih tvari iz kombiniranog lijeka s analgetičkim učinkom koji se na našem tržištu prodaje pod zaštićenim imenima Plivadon® i Caffetin® (slika 3.). Jedna tableta Plivadona® sadržava 250 miligrama propifenazona, 210 miligrama paracetamola, 25 miligrama kofeina i 10 miligrama kodeina, a u tableti Caffetina® je 210 miligrama propifenazona, 250 miligrama paracetamola, 50 miligrama kofeina i 10 miligrama kodeina (12).

Analiza tjelesnih tekućina, tkiva, kose i zuba obavljena je na plinskomasenom kromatografu Agilent 5973N MSD (Agilent Technologies, Palo Alto, California, SAD).

Plinskom kromatografijom, tehnikom head space Perkin Elmer AutoSystem Gas Chromatograph s TurboMatrix 40 (Perkin Elmer, Waltham Massachusetts, SAD) pronađeno je u krvi 0,00 g/kg apsolutnog alkohola.

Tablete Plivadona® i Caffetina® pojedinačno su otopljene u 5 mL destilirane vode. pH vrijednost tako pripravljenih otopina bila je 5,5.

- In blood - 0.66 mg% of propyphenazone, 1.50 mg% of caffeine and traces of codeine;
- In urine - 0.11 mg% of propyphenazone, 1.50 mg% of caffeine, 0.26 mg% of codeine and traces of paracetamol;
- In bile fluid – 1.03 mg% of propyphenazone, 1.24 mg% of caffeine, 0.06 mg% of codeine and traces of paracetamol;
- In liver and kidney tissue, the presence of propyphenazone, caffeine, codeine and paracetamol was identified.

Hair and gastric content samples were extracted using an organic solvent, and the obtained extracts were analyzed by a gas chromatograph coupled to a mass detector to identify as follows:

- The hair contained propyphenazone and traces of codeine;
- The gastric contents contained propyphenazone, caffeine, codeine and paracetamol.

The quantifiable concentration of active constituents of the compound drug showed to be within a therapeutic range.

A tooth, weighing 0.86 gram, was pulverized by a mixer mill MM 301 (Retsch, GmbH & Co. KG., Haan, Germany) for one minute. The powdered tooth material was extracted with 5 mL methanol, centrifuged, and filtered using Blue Ribbon filter paper (Munktell 90 mm/391). The remaining powdered tooth tissue was extracted with 5 mL ethyl acetate, centrifuged and filtered through a blue ribbon filter into the same collection receptacle together with the previous extract. The obtained analyte was evaporated to a small volume and was bluish in color. Such analyte was then silinated/derivatized with 30 µL BSTFA+1%TMCS at 70°C for 30 minutes. This procedure complies with the validation procedure used by Pellegrini and colleagues to extract opiates and cocaine from human teeth (11).

Gas chromatography with mass spectrum detection carried out on the silinated/derivatized tooth extract confirmed the presence of propyphenazone, paracetamol, caffeine and codeine – i.e. pharmacologically active constituents of compound medications with analgesic effect, available on the Croatian market under the registered trademarks as Plivadon® and Caffetin® (Figure 3). One tablet of Plivadon® contains 250 mg of propyphenazone, 210 mg of paracetamol, 25 mg of caffeine and 10 mg of codeine, whereas a Caffetin® tablet contains 210 mg of propyphenazone, 250 mg of paracetamol, 50 mg of caffeine and 10 mg codeine (12).

Analysis of body fluids, tissues, hair and teeth was carried out on an Agilent 5973N MSD gas chromatograph / mass spectrometer (Agilent Technologies, Palo Alto, California, USA).

Headspace-gas chromatography carried out on a Perkin Elmer AutoSystem Gas Chromatograph equipped with TurboMatrix 40 (Perkin Elmer, Waltham Massachusetts, USA) showed 0.00 g/kg of absolute alcohol in the blood.

Plivadon® and Caffetin® tablets were each dissolved in separate 5 mL vials of distilled water. The pH value of thus prepared solution was 5.5.

Rasprava

Zakon u Republici Hrvatskoj nalaže obdukciju kada na temelju medicinske dokumentacije nije moguće zaključiti što je uzrok smrti, a osoba je umrla tijekom prijma u zdravstvenu ustanovu (13). Takve okolnosti bile su i u ovom slučaju. Osim toga, raspoloživi podaci potaknuli su i pitanje nasilne smrti zbog moguće povezanosti smrtnog ishoda i dugogodišnje ovisnosti o lijekovima, što također predstavlja indikaciju za sudskomedicinsku obdukciju (14).

Prema uputama proizvođača tableta Plivadon® i Caffetin® (15, 16) ti kombinirani analgetici imaju i antipiretički učinak, no u Registru lijekova kao djelovanje se navodi samo analgezija (12). Aktivne komponente paracetamol i propifenazon sinergistički djeluju inhibicijom ciklooksigenaze – enzima odgovornog za sintezu prostaglandina. Kodein također ima analgetsko i blago sedativno djelovanje, a kofein poboljšava apsorpciju lijeka (15, 16).

Kemijsko-toksikološkom analizom ustanovljena je prisutnost svih farmakološki aktivnih tvari navedenih lijekova u biološkim uzorcima – u mokraći, žučnoj tekućini, tkivu jetara i bubrega, želučanom sadržaju i ekstraktu zuba. Pojedine aktivne komponente pronađene su i u uzorcima krvi i kose. Kako su oba lijeka gotovo istovjetnog sastava, nije bilo moguće razlučiti koji je od njih bolesnik uzimao. U svakom slučaju nalaz se poklapa s heteroanamnestičkim podatkom o dugogodišnjem korištenju visokih doza Plivadona® (i do 40 tableta na dan).

Popratne pojave pri korištenju paracetamola u terapijskim dozama su rijetke. No, poznato je da velike količine mogu potaknuti nekrozu jetara, za što je otkriven i mehanizam (17). Dobro je poznata i nefrotoksičnost visokih doza paracetamola (18). Manje je poznato da stalno uzimanje povećanih doza može rezultirati razvojem toksičnog hepatitisa (19) i gastrointestinalnim komplikacijama poput erozija, vrjedova, krvarenja i perforacija (20–22). Navedene kronične komplikacije, kao posljedica uzimanja visokih dnevnih doza paracetamola, potvrđene su i u opisanom slučaju – pronađen je kronični hepatitis, želučane erozije i vrijed na dvanaesniku. Klinički simptomi su mučnina, povraćanje, anoreksija, gubitak tjelesne mase i dehidracija (23). Zato se i opća pothranjenost uočena na liječničkom pregledu može povezati s kroničnim uzimanjem kombiniranih lijekova kao što su Plivadon® i Caffetin®.

Propifenazon je derivat pirazolona (24). Ta se skupina lijekova rabi već godinama godina (24), a slučajevi akutne intoksikacije s letalnim ishodom rijetki su i uglavnom se događaju u dječjoj dobi (25, 26). Smatra se da su nuspojave posljedica preosjetljivosti na lijek, a da nisu u vezi s količinom uzetoga lijeka (25, 27). Kao reakcije preosjetljivosti u literaturi se navode anafilaktički šok, kožne i respiratorne reakcije, agranulocitoza i vrućica (27). U opisanom su slučaju medicinski podaci o bolesniku bili vrlo oskudni i nisu upućivali na razvoj reakcija preosjetljivosti. Histološkom analizom ustanovljeno je da je koštana srž hipocelularna, s oskudnim stanicama hematopoeze i mijelopoeze. Oskudna mijelopoeza mogla je, uz opću pothranjenost, pridonijeti razvoju gangrenozne i apscedirajuće upale pluća koja je bila i uzrok smrti.

Discussion

The current legislation of the Republic of Croatia requires an autopsy in the circumstances when the cause of death cannot be determined by medical records, and the individual died at admission to a health care facility (13). Such circumstances were also present in this case. In addition, the available data raised questions about violent death because of a potential relationship between the fatal outcome and suspected medication addiction, which is also an indication for medico-legal autopsy (14).

According to information leaflets by the Plivadon® and Caffetin® manufacturers (15, 16), these compound analgesics also have anti-pyretic effect, while in the Register of Medicinal Products only their analgesic action is included (12). Active ingredients such as paracetamol and propyphenazone interact to produce synergistic inhibition of cyclooxygenase – an enzyme that is responsible for the synthesis of prostaglandins. Codeine also has both analgesic and mild sedative actions, whereas caffeine increases the absorption of an analgesic (15, 16).

Chemical toxicity testing revealed the presence of all pharmacologically active ingredients of the above medications in biological samples, including urine, bile fluid, liver and kidney tissues, gastric contents and teeth extracts. Some active components were also found in both blood and hair samples. Since the composition of both drugs is almost the same, it was not possible to identify which of the two was being used. In any case, the results comply with hetero-anamnestic information about the long-term use of large doses of Plivadon® (even up to 40 pills per day).

Side effects of paracetamol used at therapeutic doses are rare. However, high doses are known to potentially induce liver necrosis, and the mechanism has already been identified (17). Nephrotoxicity by high doses of paracetamol is also well known (18). However, it is less known that chronic intake of high doses can lead to the development of toxic hepatitis (19) and gastrointestinal complications such as erosions, sores, bleeding and perforation (20-22). The above chronic complications resulting from large daily doses of paracetamol were also identified in this case report where they led to the development of chronic hepatitis, gastric erosions and duodenal ulcer. The clinical symptoms include nausea, vomiting, anorexia, loss of body mass and dehydration (23). Therefore, general undernutrition diagnosed on examination can be associated with the chronic intake of compound medications such as Plivadon® and Caffetin®.

Propyphenazone is a derivative of pyrazolone (24). This group of medications has been widely used for many years (24), and cases of acute intoxication with a lethal outcome are rare and occur mostly in childhood (25, 26). It is thought that the side effects are due to a hypersensitivity reaction to the medication rather than the amount of the drug taken (25, 27). Hypersensitivity reactions reported in the medical literature have included anaphylactic shock, skin reactions, respiratory reactions, agranulocytosis and fever (27). In the described case, information contained in the patient's medical records was very poor and did not suggest that there might

Ovisnost o kodeinu već je dugo poznata (28), a u literaturi se posljednjih godina opisuju slučajevi ovisnosti o kombiniranim lijekovima s analgetičkim i antipiretičkim učinkom koji sadržavaju kodein kao jednu od komponenti (29–31). Zato se može zaključiti da bi i konkretan slučaj mogao biti primjer takve ovisnosti. Naknadno je od obitelji dobiven podatak da je pokojnik u mladosti počeo uzimati lijekove zbog povremenih zubobolja i glavobolje, da bi s vremenom razvio ovisnost o lijekovima.

Suprotno literaturnim podacima koji se odnose na akutne i kronične promjene na organima u slučaju uzimanja visokih doza kombiniranih analgetika, u dostupnoj literaturi nismo našli podatke o mogućem utjecaju tih lijekova na zube. Nakon obavljene kemijsko-toksikološke analize nedvojbeno je dokazana prisutnost svih aktivnih komponenti u ekstraktu zuba (slika 5.). Ta činjenica upućuje na to da zub može biti prikladan za izolaciju potencijalno toksičnih tvari koje se dulje unose u organizam. Dosad se u literaturi navodila samo ekstrakcija opijata i kokaina iz ljudskih zuba (9, 32).

Učinak na zube i usnu šupljinu može se promatrati s razine lokalnog i općeg djelovanja lijeka.

Lokalnim unosom tableta u usnu šupljinu podiže se razina kiselosti, što se smatra glavnim vanjskim čimbenikom za nastanak zubnih erozija. Već je navedeno da otopina tableta Plivadona® i Caffetina® ima pH 5,5. Osim djelovanja kisele otopine na površinu zubne cakline, lijek se može primijeniti i tako da se tableta (ili čak djelomice otvorena tableta s folijom) uloži u predvorje usne šupljine – prostor između usnice i usnene plohe zuba. Na taj način bi, uz kemijsko djelovanje, moglo nastati i mehaničko oštećenje zuba. Zajednički učinak tih dvaju mehanizama najvjerojatnije je odgovoran za specifične erodirane lezije usnenih ploha zuba, uglavnom gornjih.

Tijekom kemijsko-toksikološke analize uočena je plavkasta boja otparenog ekstrakta zuba. To nameće zaključak da bi aktivne komponente kombiniranog analgetika (Plivadon®, Caffetin®) tijekom kontinuirane primjene u visokim dozama mogle ljubičasto-plavkasto diskolorirati zube. Specifična građa zubne pulpe i dentina te mogućnost prolaska i deponiranja aktivnih komponenti kombiniranog analgetika, omogućila je njihovo dugotrajno odlaganje u dentinskim kanalićima, a time i eventualni nastanak diskoloracije.

Opće djelovanje lijeka odnosi se na štetne učinke paracetamola (acetaminofena) koji su mogli potaknuti kronični hepatitis, želučane erozije i vrijed na dvanaesniku. Simptomi tih bolesti uzajamno se preklapaju, a jedan od njih – povraćanje, predstavlja unutarnji kemijski čimbenik koji je mogao pridonijeti pojavi erozija.

Posebice upućujemo na proces izolacije analgetika iz zuba, kao na moguću dopunsku metodu u utvrđivanju dugotrajne prekomjerne uporabe tih vrsta lijekova.

be a risk of developing hypersensitivity reactions. Histological analysis showed the bone marrow hypocellularity, with abnormally low number of hematopoietic and myelopoietic cells. Reduced myelopoiesis, together with general undernutrition, could have played a role in the development of gangrenous, abscessing pneumonia which, in this case, was determined to be the cause of death.

Addiction to codeine has long been recognized (28), and the recent literature also describes cases of dependence on compound drugs with analgesic and antipyretic properties, containing codeine as one of the ingredients (29-31). It can therefore be concluded that this particular case may provide an example of such dependence. In addition, the family provided information that the patient had started taking medications for occasional toothaches and headaches in adolescence, to develop dependence on these medications over time.

In contrast to literature data about acute and chronic changes of the organs resulting from the use of large doses of compound analgesics, no information about potential effects of these medications on teeth has been found in the available literature. Chemical toxicology analysis provided definite evidence for the presence of all active ingredients in the tooth extract (Figure 5). This fact therefore suggests that the tooth can provide adequate material for the isolation of potentially toxic substances that are taken into the body over a long period of time. The literature to date reports only on the extraction of opiates and cocaine from human teeth (9, 32).

The effects on teeth and the oral cavity can be observed at the level of both the local and systemic action of the drug.

Local administration of tablets into the oral cavity increases the acidity level, which is considered to be the major external risk factor for the development of tooth erosion. It has already been said that the solution of Plivadon® and Caffetin® tablets has a pH of 5.5. In addition to the effect of an acidic solution on a tooth enamel surface, the drug can also be administered via the oral route with the tablet (or even the tablet together with its foil only partially opened) placed in the upper oral vestibule – the space between the upper lip and the labial surface of the tooth. In addition to the chemical effect, this mode of administration can produce mechanical damage to teeth. The mutual action of these two mechanisms is most likely responsible for the formation of specific eroded lesions of the labial surface of teeth, especially in the upper jaw.

During chemical toxicology testing of teeth, a bluish color to the evaporated tooth analyte was observed. This leads to the conclusion that the active ingredients of the compound analgesic (Plivadon®, Caffetin®) during continued administration of large doses could cause purple-bluish tooth discoloration. The specific structure of dental pulp and dentine, and the potential passage and deposition capacity of the compound analgesic active ingredients enabled their long-term disposal into the dentinal tubules, and made possible the development of discoloration.

The systemic action of the drug refers to the adverse effects of paracetamol (acetaminophen) that can lead to chronic hepatitis, gastric erosions and duodenal ulcer. The symp-

toms of these diseases overlap, and one of them, i.e. vomiting represents an intrinsic chemical factor that may have contributed to the development of erosions.

The procedure of isolation of an analgesic drug from the tooth is suggested to be a useful ancillary method for determining the long-term excessive use of analgesic drugs.

Zaključak

Na temelju opisanog slučaja autori zaključuju da je kombinirani analgetik kemijskim i mehaničkim djelovanjem uzrokovao vrlo specifične erozije na usnenim dijelovima zuba i ljubičasto-plavkastu boju zuba.

Aktivne komponente kombiniranog analgetika pronađene su u ekstraktu zuba, što dokazuje da je zub pogodan za kemijsko-toksikološku analizu metodom plinske kromatografije.

Autori ističu važnost interdiciplinarnog rada u rješavanju forenzičnih slučajeva.

Conclusion

Based on this case report, the authors conclude that the compound analgesic, by both its chemical and mechanical action, caused very specific erosions on the labial surface of the teeth and the observed purple-bluish color development in the teeth.

The active ingredients of the compound analgesic were identified in the tooth extract, which proves that the tooth is an adequate organ for chemical toxicology analysis by gas chromatography.

The authors demonstrate the importance of interdisciplinary collaboration in solving forensic cases.

Abstract

Dental erosion is currently the most common non-carious change on the tooth resulting from long-term effects of acidic chemical (pH<7) factors on the tooth surface without the intervention of bacteria. These factors can be divided into intrinsic and extrinsic factors (1-3). The intrinsic chemical factors include acidic gastric contents reaching the oral cavity as a result of vomiting, whereas the extrinsic factors are any acidic substances taken into the mouth, primarily some types of foods and beverages and some medicines. The aim of this report was to show potential effects of a compound drug with analgesic properties (active ingredients - paracetamol, propyphenazone, codeine phosphate and caffeine) on changes occurring in the teeth. This paper describes very specific erosions on the labial portions of the teeth and the occurrence of purple-bluish tooth color found at autopsy of a 35-year-old severely malnourished man who died at admission to hospital treatment. Hetero-anamnestic information about a long-term dependence on a compound analgesic was provided. In addition to tooth changes, the autopsy showed erosions of the gastric mucosa, chronic ulcer in the duodenal region, chronic liver inflammation, and bone marrow hypoplasia. The cause of death was bilateral purulent inflammation of the lungs with an extensive gangrenous focus in the left lobe. Chemical toxicology analysis revealed the presence of all pharmacologically active ingredients in urine, bile fluid, liver and kidney tissues, gastric contents and teeth extracts. Long-term dependence on the compound analgesic as a probable mechanism for the development of tooth and other organ changes has been discussed. The paper stresses the importance of the tooth that in our example proves to be an adequate organ for toxicology analysis by gas chromatography, and the importance of interdisciplinary collaboration in solving forensic cases. Additionally, isolation of analgesic from the tooth is suggested to be a helpful diagnostic method in cases of suspected abuse of medicinal drugs.

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