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RESEARCH ARTICLE

HISTOPATHOLOGICAL AND BIOCHEMICAL EFFECTS OF TEETHING MIXTURE SYRUP AND TEETHING POWDER ON THE GASTROINTESTINAL TRACT, LIVER, KIDNEYS AND LUNGS OF WISTAR RATS

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Histopathological, teething syrup, teething powder, gastrointestinal tract, liver. Abbreviations: TM – Teething Mixture Syrup. TP – Teething Powder.

ABSTRACT

Objectives: Pathological effects of teething mixture syrup (par aminophenol and diphenhydramine hydrochloric acid) and teething powder (*Matricaria recutita*) on the gastrointestinal tract, lungs, liver and kidneys of wistar rats.
Study design: Fifty four adult wistar rats of both sexes, were divided into six groups of nine rats per cage. Group A served as control, groups B, C and D received half doses 0.42(ml/kg body weight), normal dose 0.83(ml/kg body weight) and double dose 1.67(ml/kg body weight) of teething mixture syrup while groups E and F received normal dose 0.67(mg/kg body weight) and double dose 1.33(mg/kg body weight) of teething powder respectively. Three rats were sacrificed from each group at three weeks intervals, for histopathology studies and biochemical analyses.
Results: Revealed significant decrease in the percentage mean body weight increase of all the groups that received teething powder, ($P<0.001$). Histomorphologic changes occured in the stomach, liver and kidney of the rats treated with normal and double doses of both teething substances. Biochemical analyses revealed significant increase in the serum total billirubin and alkaline phosphatase activities of the rats treated with both teething substance ($P<0.05$).
Conclusion: The administration of both teething substances revealed dose and duration related adverse effects.

INTRODUCTION

Teething is the first growth of teeth or the phenomena accompanying the growth of teeth through the gum in children (Encyclopedia Britannica, 2008). Teething or teethe differ from teethed teething which refers to experiencing of the back formation of teeth. The period of teething could be uncomfortable both for the child and the parents, but some babies and toddlers feel more miserable than others. Episodes could begin as early as two months of age but occur at around six to seven months of age. Babies usually experience some problems of teething which includes, increased drooling, restlessness or decreased sleeping, refusal of food, irritability or fussiness, biting, chewing or sucking of hands or fingers, rubbing of cheeks, a mild rash around the mouth area (due to excess saliva). The stress and discomfort of teething can lower a child's resistance to infection, spitting up of swallowed saliva or mild diarrhea can occur without infection but fever and symptoms of actual illness are not "just teething" unlike the common conception of teething in this part of the world that teething is accompanied by diarrhea and fever (Bankole *et al.,* 2003; Ezechukwu *et al.,* 2004 and Ene-Obong *et al.,* 2008).To ease the pains and discomfort of teething several measures which include, a damp or frozen wash cloth or a cold teething ring filled with water can help numb the area, counter pressure or gentle rubbing of the gum with a clean damp cloth may help, cold food have been adopted. Other remedies include the use of teething power and teething mixture syrup which come in different forms and composition. It can be homeopathic or chemical substances in form of drugs. The common ones in Enugu metropolis and Eastern part of Nigeria includes, Piccan®, Bonababe®, Finebaby®, Babyrex®, Babyrex®, Ashton and Parson®. Homeopathic remedies are the common and current remedy applied in the western countries where as in this part of the world chemically constituted teething powders are commonly used (Ezechukwu *et al.,* 2004). The death of 84 babies in different parts of Nigeria between November and December 2008 due to use of a certain brand of teething power mixture syrup "My pikin®" also confirm the regular use of drug teething mixture in Nigeria (Yinka, 2008 and Howden, 2007). *Chamomilla (Matricaria recuta)* is the most widely used relaxation herbs in the western countries (Ermasherbs, 1998). Teething powder mixtures like Piccan®, Babyrex®, Bonababe®, Finebaby® produced and used

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in Nigeria contains paracetamol (acetaminophen) and diphenhydramine HCl as the active components but in different concentrations. Overdose of par aminophenol is known to cause hypersensitivity, gastric precipitation, induce kidney toxicity and hepatotoxicity (Ucheya and Igweh, 2006). Diphenhydramine is used as antihistamine (Hl) drug but have side effect of sedation in children at normal dose. At very high toxic dose levels, marked stimulation, agitation and even convulsion may precede coma.

Justification

Most teething remedies have indications and contraindications on the gastrointestinal tract, liver and kidney, but more emphasis will be laid on the Nigeria produced and used teething power and teething mixture syrup. The demise of over eighty four children who were given a tainted teething power "My Pikin ®" in 2008 calls for more research on the drug teething mixture syrup and teething powder. The children were brought to fever, convulsion, diarrhea and vomiting and unable to urinate and finally died of acute renal failure. The teething mixture when analyzed contained diethyl glycol used as antifreeze and brake fluid (Amira, 2008).

Aim

To assess the histopathological and biochemical effects of teething powder and teething mixture syrup on the GIT, liver, kidney and lungs of Wistar rats.

Objectives

- Assessment of the effects of different doses and durations of administration
- To enlighten the public more on teething.

MATERIALS AND METHODS

Structured self administered questionnaire was used to sample mothers' experience, to know the common teething mixture syrup or teething powder used in our locality. The duration and dose administered was also ascertained to guide the research. Fifty four (54) Wistar rats aged between 3 - 4 months, weighed 240 – 340 gram was procured from the animal house of Faculty of Veterinary Medicine, University of Nigeria Nsukka. The rat comprised of 27 males and 27 females were acclimatized for two weeks in the Animal House. They were fed on starter feed pellet (Guinea feed®) and water *ad libitum*. They were housed in a bottom wired metal cages measuring 90cm and 90cm by 30cm and allowed for constant light schedule (12 hours light and 12 hours darkness cycle). Group identification was done by number strokes marked on their tail with permanent marker. The rats were handled according to the international ethics on animals.

Design and Conduct of Research

Male and female rats were used together in this research since research had shown no significant difference in the clinical parameter between the sexes (Payasi *et al.,* 2010). The rats were divided into six groups. Groups A – F comprised of nine rats each according to sex, age, and approximate body weight. The weights of the rats were recorded a day before commencing intervention. Group-A, comprised of 9 males, served as the control group. Groups B, C, and D comprised of 9 females, 9 females and 9 males, received half dose 0.42(ml/kg body weight), normal dose 0.83(ml/kg body weight) and doubled dose 1.67(ml/kg body weight) respectively of teething mixture syrup (TM) (Bonabeb®) with respect to normal dose for babies. Groups-E and F comprised of 9 females and 9 males, received normal dose 0.67(mg/kg body weight) and doubled dose 1.33(mg/kg body weight) respectively of teething powder (TP) (Ashton and Parson®) with respect to normal dose for babies. A known quantity of teething powder was dissolved in a known quantity of their drinking water. The substances were administered using metal oral cannular and automatic pipette. The weight of a baby at 3 months was estimated with the formula (N + 9)/2 kg, where N is equal to age of the baby in months, hence the weight was estimated as 6kg. For the teething mixture (Bonabebe®), the normal dose for the baby is 5ml three times daily. Each 5ml contains 120mg of par aminophenol and 6.25mg of diphehydramine which are the active agents of the syrup. For the teething powder (*Matricaria*), Ashton and Parson®, the dose is 4mg twice daily. During the period of treatment the rats were observed regularly for overt physical changes. At intervals of 3 weeks, of intervention, three (3) rats from each group were selected at random after over-night fast. There weights were recorded then they were anaesthetized using chloroform swab in a covered container and sacrificed. The blood was collected by cardiac puncture into plain tube, Li heparinised and fluoride oxalate anticoagulant bottle for biochemical analysis. Organs of interest were removed and preserved in 10% formal saline for histopathology studies.

Physical parameters

Physical parameters included body weight, food and water intake, tremor, excitation, sedation/weakness were studied. Mortality was also recorded and autopsy was to be done on the rat.

Histopathology Examination

The liver, kidneys, lung, stomach, small intestine and large intestine were dissected out, preserved and fixed in well labeled containers of 10% formal saline for later histology study. The tissues were auto processed and stained with Haematoxylin and Eosin technique following the Standard Operating Procedure.

Clinical chemistry parameters

Aspartate Transaminase (AST) or Serum Glutamic Oxaloacetate transaminase (SGOT), Alanin Transaminase (ALT) or Serum Glutamic Pyruvate transaminase (SGPT) and Alkaline phosphatase (ALP) activities, total plasma protein, Total Bilirubun, fasting glucose level, Creatinine and Serum Electrolytes were estimated. The results were recorded in triplet as mean ± SEM. One way analysis of variance single factor was used and paired student t – Distribution to compare the control to each group. Both intervened groups were also compared. Microsoft excel® package was used for the statistical analysis. $P < 0.05$ was significant.

Analytical Procedures

- **Physical Procedure:** The weight of animals were recorded using electronic weighting balance and other physical parameters were obtained by constant and close examination

Table 1. Mean percentage rate of weight increase.

	GP A	GP B	GP C	GP D	GP E	GP F
3 WKS	13.34	10.19	3.32*	4.38*	2.49*	3.31*
6 WKS	7.79	0.72*	7.88	5.04	1.14*	1.57*
9 WKS	13.90	11.90	3.79*	11.82	4.57*	-3.49*

*significant change

Table 2. Histopathology result for animals treated with teething mixture syrup for 6 weeks

GROUP\ ORGAN	GROUP A	GROUP B	GROUP C	GROUP D
STOMACH	Normal	Normal	Slough of epithelial lining	Slough of epithelial lining
LIVER	Normal	Normal	Stromal proliferation and Nodules in some areas	Stromal proliferation and fibrosis
KIDNEY	Normal	Normal	Mild edema and glomerulus adherence to Bowman's capsule	Edema and glomerulus adhere to BC
LUNGS	Normal	Fibrosis in one of the animals	Normal	Normal
SMALL INTESTINE	Normal	Normal	Normal	Normal
LARGE INTESTINE	Normal	Normal	Normal	Normal

Table 3. Histopathology result for animals treated with teething mixture syrup for 9 weeks

GROUPS\ ORGANS	GROUP A	GROUP B	GROUP C	GROUP D
STOMACH	Normal	Normal	Slough of epithelial lining	Slough of epithelial lining
LIVER	Normal	Normal	Nodules	Fibrosis and proliferation
KIDNEY	Normal	Normal	Glomerulus adhere to BC and edema	Glomerulus adhere to BC
LUNGS	Normal	Normal	Normal	Normal
SMALL INTESTINE	Normal	Normal	Normal	Normal
LARGE INTESTINE	Normal	Normal	Normal	Normal

- **Histopatholgical Procedure:** The fixed organs (liver, kidney, stomach, small intestine, large intestine and lungs) were cut into slices of about 5mm, auto-processed by standard histological method, embedded in paraffin wax, sectioned using Rotary microtome and picked on slide. The sections were stained using Haematoxylin and Eosin technique (Ehrlich, 1886 and Baker and Silverton, 1985). The processed tissues were sent to Pathologist for microscopy and photomicrographs taken.
- **Clinical chemistry Procedure:** The two biochemical tests were Liver Function Test (LFT) and Renal Function Test (RFT).

LFT: RANDOX® kit was used for the SGOT or Aspartate Transaminase (AST) and SGPT or Alanin Transaminase (ALT), Alkaline Phosphatase (ALP) activity, serum total bilirubin. RANDOX® kit was used for plasma total protein and Fasting Blood Sugar (FBS).

RFT: RANDOX® kit was used for serum creatinine estimation.

Electrolyte: The electrolytes estimation was done using Ion Selective Electrode (ISE) autoanalyser principle (Burtis and Ashwood, 1997).

RESULTS

Food and water intake by the rats were not affected in any of the group. There was no sign of tremor or excitation in all the groups. There was a marked sign of sedation in all the groups treated with teething syrup or teething powder. The rats usually appeared calm and drowsy, 30 – 60 minutes after the administration of test substance. Prolonged labor occurred in one of the treated rats that gave birth and fetuses were still born. No death was recorded during the research.

Clinical Chemistry Results

Glucose: No significant changes, $P > 0.05$ in all the treated groups compared to the control.

Plasma Total Protein

- Significant decrease, $P < 0.05$ occurred after 3 weeks in groups D and F.
- No significant changes occurred in all the treated groups after 6 weeks
- Significant decrease, $P < 0.01$ occurred in groups C, D, and E after 9 weeks.
- Significant increase, $P < 0.05$ occurred in group F after 9 weeks.

Serum total bilirubin

- Significant increase, $P < 0.05$ occurred after 6 weeks in groups B, C, D and F.
- No significant changes, $P > 0.05$ in all the treated groups after 9 weeks.

Alkaline Phosphatase (ALP) activity

- Significant increase, $P < 0.05$ occurred after 6 weeks in group F.
- Significant increase, $P < 0.05$ occurred after 9 weeks in groups D and E.

Aspartate transaminase (AST/SGOT)

- Significant increase, $P < 0.05$ occurred after 6 weeks in group F.
- Significant increase, $P < 0.05$ occurred after 9 weeks in groups D and E.

Table 4. Histopathology result for rats treated with teething powder for 3 weeks

GROUPS/ ORGANS	GROUP E	GROUP F
STOMACH	Slough of epithelial lining	Slough of epithelial lining
LIVER	Numerous cystic spaces	Fibrosis
KIDNEY	Mild glomerular adherence to BC	Mild glomerular adherence to BC
LUNGS	Normal	Normal
SMALL INTESTINE	Normal	Normal
LARGE INTESTINE	Normal	Normal

Table 5. Histopathology results for rats treated with teething powder for 6 weeks

GROUPS\ ORGANS	GROUP E	GROUP F
STOMACH	Slough of epithelial lining	Slough of epithelial lining
LIVER	Cystic spaces	Nodules and mild proliferation
KIDNEY	Mild areas of glomerulus adherence to BC	Mild glomerulus adherence to BC
LUNGS	Normal	Normal
SMALL INTESTINE	Normal	Normal
LARGE INTESTINE	Normal	Normal

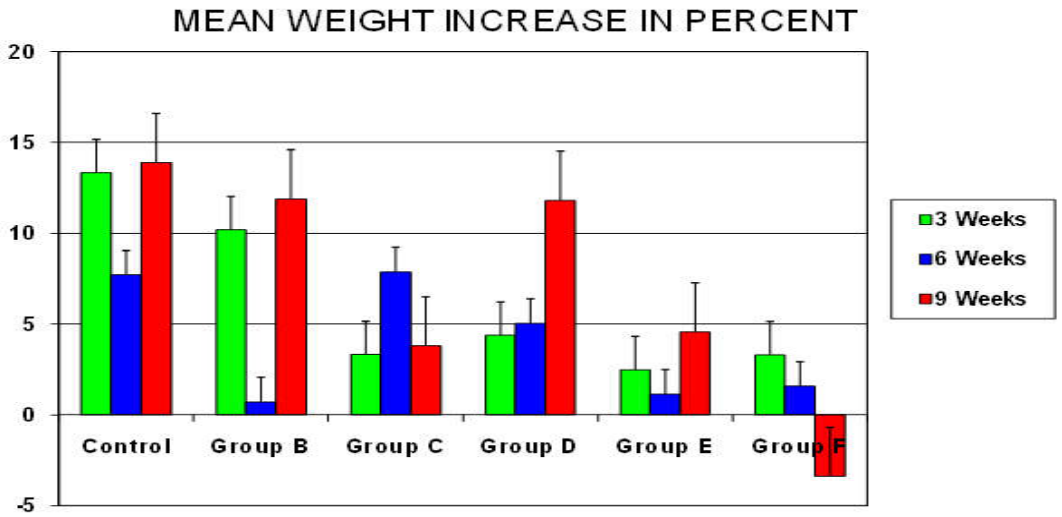
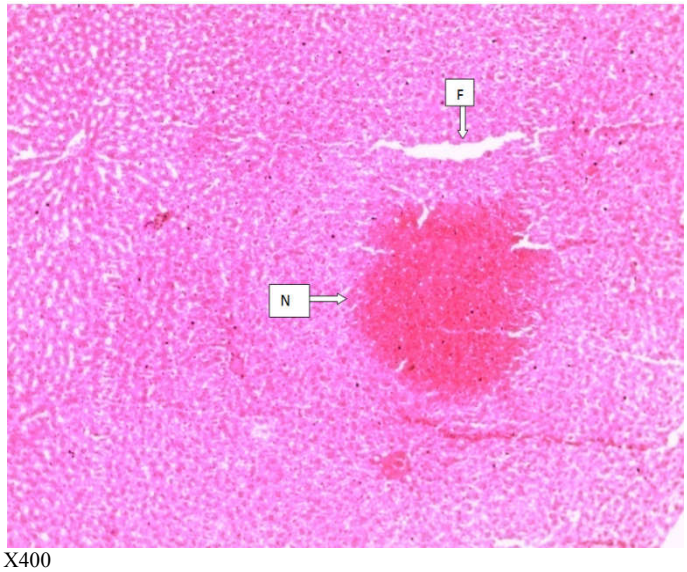
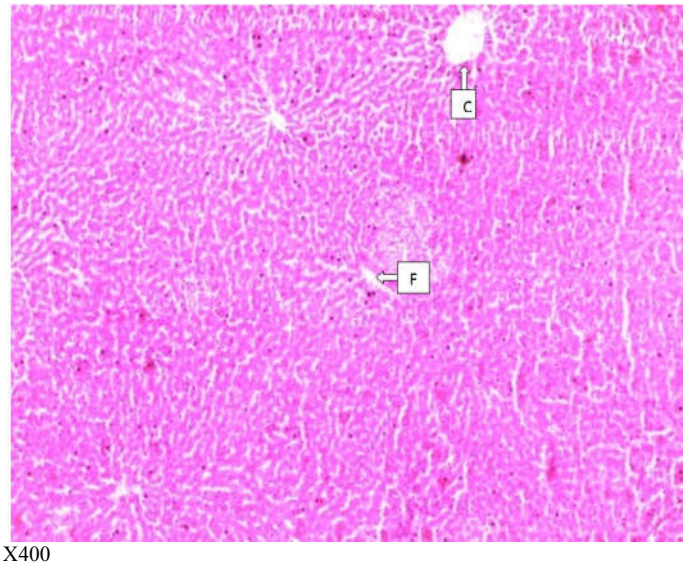


Figure 1



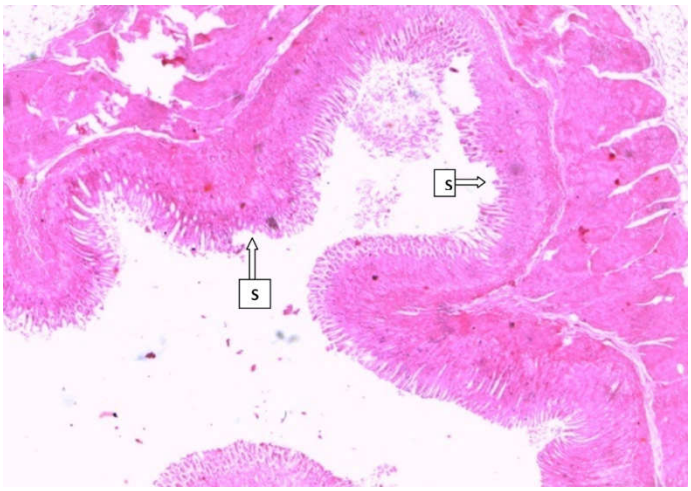
X400
Photomicrograph shows nodule (N), fibrosis (F), stromal proliferation and loss of normal architecture of the liver.

Plate 1. Photomicrograph showing liver of rats treated with normal dose of teething mixture syrup after 9 weeks



X400
Photomicrograph shows cystic spaces (C), fibrosis (F), stromal proliferation and loss of normal liver architecture.

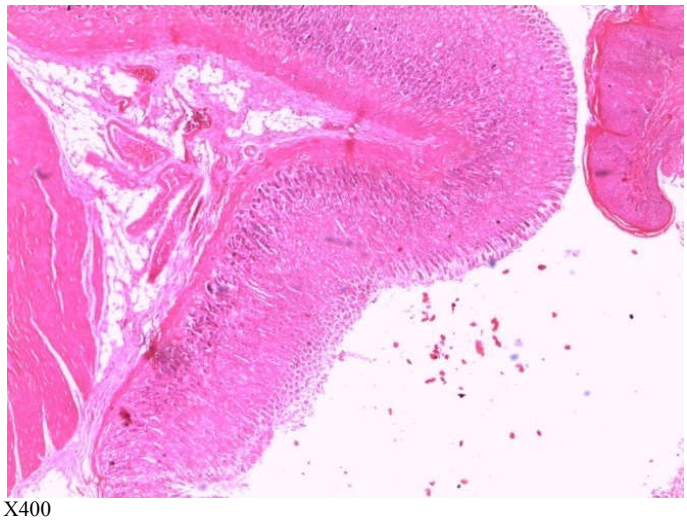
Plate 2. Photomicrograph showing the liver of rat treated with normal dose of teething powder after 3 weeks



X400
Photomicrograph shows slough of epithelial lining (S) of the mucosa and loss of intact architecture.

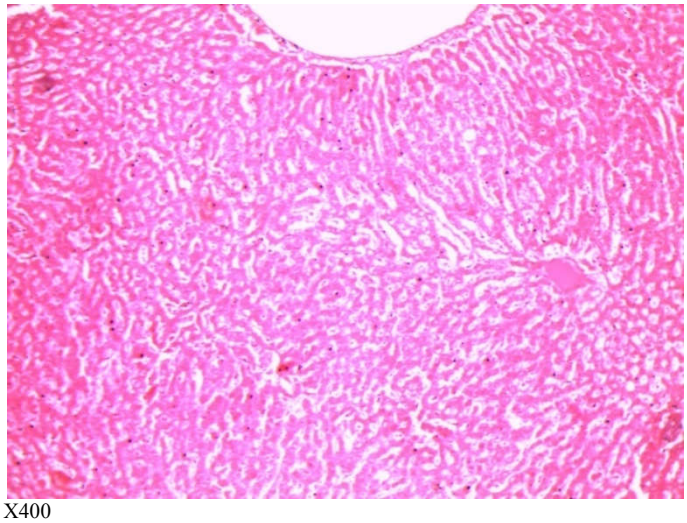
Plate 3. Photomicrograph showing stomach of rat treated with normal dose of teething powder after 3 weeks

Supplementary Materials



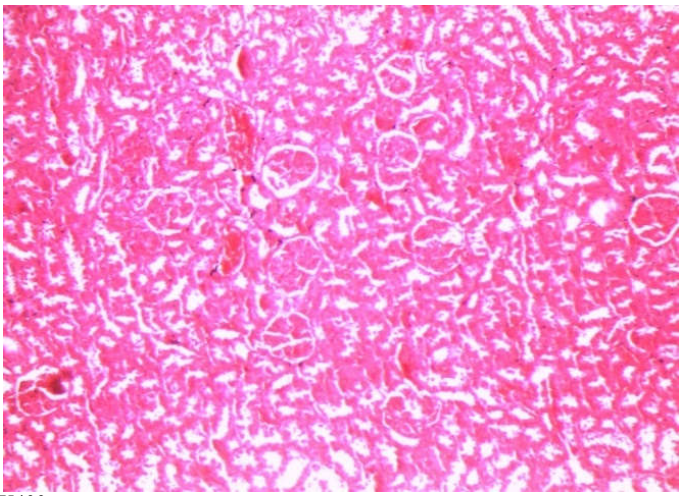
X400

Photomicrograph of stomach of control rat that received neither "teething mixture syrup" nor "teething powder"



X400

Photomicrograph of liver of control rat that received neither "teething mixture syrup" nor "teething powder"



X400

Photomicrograph of kidney of control rat that received neither "teething mixture syrup" nor "teething powder"

Alanine transaminase (ALT/SGPT)

- Significant increase, $P < 0.05$ occurred after 3 weeks in groups B, C and D. Significant decrease, $P < 0.05$ occurred after 3 weeks in group F.
- Significant decrease, $P < 0.05$ occurred after 6 weeks in groups B, D, E and F.
- Significant decrease, $P < 0.05$ occurred after 9 weeks in group F.

The Renal Function Tests showed no significant changes in all the treated rats compared to controls.

DISCUSSION

Analysis of the questionnaire showed that the common teething remedy in use is teething powder (Ashton and Parson®) as has earlier been documented (Ezechukwu *et al.,* 2004). The common teething mixture syrup in use is "Bonabebe®"; hence these remedies were used for the research. The rats after 30 – 60 minutes of treatment usually appeared calm and drowsy since the teething mixture syrup contents (Par aminophenol and diphenhydramine hydrochloric acid) and teething powder content (*Martricaria recutita)* act on the central nervous system. Diphenhydramine hydrochloric acid is classified among sedating H1 blocker (Loren *et al.,* 2010). Infusion *Chamomile* (*Martricaria recutita*) had also been used traditionally to ease colic and teething in babies and to calm restless children (Baumann, 2003). Study of the rate of mean percentage weight increase showed that significant changes occurred between the control and treated groups, which agree with the research published,"at low dose diphenhydramine HCl caused weight loss or decreased weight gain (Cosmetic safety reviews 2011). The effect was more pronounced among the group treated with teething powder compared to those treated with teething mixture syrup. Aqueous and methanol Chamomile extracts specifically reduce cellular proliferation and enhanced induction in apoptosis in various cancer cells (Srivastava and Gupta, 2007). These effects could lead to reduction in weight gain in babies or even under weight which might be wrongly attributed to malnutrition. The histopathology effects revealed dose and duration of administration dependence. There was no slough of mucosal epithelium of the stomach in group treated with

half dose of teething mixture syrup but the group treated with normal and double dose of both teething mixture syrup and teething powder showed slough which is a typical sign of ulcer. Slough was mild in normal doses but more prominent in the double dose treated rats. The result is in accordance with the warning against contraindications by the manufacturers and as documented in previous research,"the liver necrosis from par aminophenol" which they found out sub mucosal capillary-venous congestion and occasional ulcer on the cardiac and pyloric region of stomach of rats treated with paracetamol (Boyd and Bereczky, 1966). On examination of the small and large intestine, the treated and control group showed intact architecture and this equally correlate with Boyd and Bereczky 1965 where they noted just minor capillary congestion and normal architecture of the intestine (Kumar *et al.,* 2007). Histopathology study of the liver showed proliferation of stromal tissue, hyper pigmentation, vacuolation, fibrosis and hyalinization in the groups treated with normal and double doses of teething mixture syrup and teething powder. Proliferation of stroma and hyper pigmentation are sign of inflammatory response and necrosis which is in line with the significant increase in serum total bilirubin and alkaline phosphate activity as noted (Burtis and Ashwood, 1997 and Kumar *et al.,* 2007). Vacuolation or cystically dilated spaces are sign of centrilobular necrosis. Hyalinization is a typical sign of recovery from inflammation. Significant decrease in plasma total protein of rats treated compared to control group could be due to hepatic dysfunction since the liver extensively synthesis protein at normal function. Significant increase in plasma total protein of rats treated with double dose of TP after 9 weeks of treatment could be due to increase in γ-globulin fraction of plasma protein following stimulation of extrahepatic reticuloendothelial system. This occur due to antigen shunt from the intestine through hepatic portal vein because chronic hepatitis which causes reduction in liver reticuloendothilial function (Burtis and Ashwood, 1997).

Histopathology of the kidney showed mild effect on the kidney compared to the liver and this had since been reported that renal effect of par aminophenol overdose are less commonly seen than hepatic effects. The overall incidence of acute renal failure in patient with par aminophenol toxicity is less than 2% (Blakely and McDonald, 1995). Renal failure usually occurs as a complication from hepatotoxicity. Renal failure occur only when 50% of the nephrone has been damaged and only at this time that the Renal function test could be useful to detect renal failure (Burtis and Ashwood, 1997). From the present research, there was no significant change in the RFT except in the group administered with double dose of teething mixture syrup, the architecture showed marked changes compared to the control and was in connection to nephrotoxicity due to high dose and duration. The research showed significant increase in serum sodium of rats treated with double dose of teething mixture. The results of our research, doesn't correlate with results documented previously, when they infused wistar rats with 16 – 66 mg/Kg body weight of par aminophenol for 28 days and they concluded that there was no significant change in histopathologic, biochemical and hematology analysis compared to control (Burtis and Ashwood, 1997). Though, their work was only on par aminophenol hence a comparative research between par aminophenol and diphenhydramine hydrochloric acid is necessary.

Conclusion

Histopathological and biochemical studies had revealed some dose and duration related adverse effects of teething mixture syrup and teething powders. Comparing the two teething remedies from the research they have almost similar effect but nonetheless *matricaria* is preferred for resolution was faster in groups treated with it.
The destruction of liver is earlier and more prominent compared to kidney destruction using both teething remedies.

Recommendation

In Nigeria, the Federal government and the health sector have not deemed it necessary to control or study the toxicity of paracetamol and teething powder, hence it's worthwhile to consider the study so that one can establish our own statistics. The symptoms showed by those babies who died in 2008 are typical of acute paracetamol and dipherhyudramine HCl toxicity however their demise could not had been due the diethyl glycol alone. From literature the carcinogenic and mutagenic effects of diphenhydramine has not been exhaustively tackled hence diphenhydramine is termed as potentially carcinogenic until proved otherwise. However more research is needed in this area. More studies need to be carried out in peadiatrics, to establish the actual effects of these "teething substances" on the weight of babies by comparing babies who receive teething remedies and those who don't receive. *Matricaria recutita* has been in use as herbal treatment for antiparasitic, analgesic, anti-inflammatory agent since 500 BC but it just got attention of scientist in 1940s, till date only very few research had been done as such one can suggest that the quantity of paracetamol, diphenhydramine and matricaria be reduced per dose since at normal doses they still have some pathologic effects. Mothers should always consult the physicians, pharmacists or health professionals before they use teething remedies to enable the health professional determine whether their baby can be placed on such remedies because a lot of pediatrics drug contain paracetamol and/or diphenhydramine HCl. However, teething is 'a natural and non harmful' process that deserves no special treatment unless otherwise the baby has other clinical presentations. Government and/or None Governmental organizations should commence or embark on awareness campaign to remove the myth placed on teething in this part of the world.

What are already known about the topic?

- The use of teething mixture syrup and teething powder is very common in our environment.
- *Matricaria recutita*, the active content of teething powder is traditionally used to ease colic, teething discomfort and to calm restleeness in babies.
- Paracetamol is known to have toxic effect on the gastrointestinal tract, liver and kidney if abused.

What this study should add

- Teething mixture syrup and teething powder at presently recommended dose have adverse effects on the gastrointestinal tract and liver. It also causes reduction in weight gain or retards growth in babies.
- The research suggests that the death of over 84 babies in Nigeria in 2008 due to intake of tainted teething

mixture syrup "My Pikin" could not just be due to the diethyl glycol as claimed but could be due to over dose of the drug constituents of the syrup since the symptoms and signs presented before death by those babies are pure related to overdose.

- The use of *Matricaria recutita* had more adverse and shorter effects compared to teething mixture syrup that had prolonged adverse effects

Acknoledgement

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Competing Interest- None

Contributorship

Ogu Cornelius Osinachi

- Researched about the topic and wrote the proposal.
- Prepared budget for the research
- Sourced for fund
- Funded the research
- Procured working materials and the wistar rats
- Carried out the intervention
- Sacrificed the rats and collected the needed tissues and blood for laboratory analysis
- Assisted in the laboratory analysis
- Assisted in the statistical analysis of results
- Writing of discussions and conclusion

Achukwu Peter

- Conceived the topic
- Supervisor of the research
- Proofread the work, starting from proposal to reference
- Budget preparation
- Funded the research
- Directed the research

Chukwu Ikechukwu JohnPaul

- Sourced for materials
- Review and writing of proposal and manuscript
- Funding of research
- Experimental contribution
- Laboratory analysis of samples
- Assisted in statistical analysis and review of write up

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