**Histological study of the effect of paracetamol on the seminiferous tubules of adult rabbits: light and electron microscopy**

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### Background

Paracetamol (acetaminophen) is a frequently used analgesic and antipyretic drug that is widely available without a prescription. Its overdose causes tissue injury, particularly in the liver.

### Aim of the work

This study was conducted to determine the effect of paracetamol on the seminiferous tubules of adult rabbits.

### Materials and methods

In this study, 18 adult male rabbits were utilized and equally divided into three groups (\(n=6\)): a control group (group I), a paracetamol low therapeutic dose group (group II), which received daily oral dose (8 mg/kg/day) for 3 weeks, and a paracetamol high therapeutic dose group (group III), which received a daily oral dose (16 mg/kg/day) for 3 weeks. Testicular specimens were obtained 1, 2, and 3 weeks from the start of the experiment and sections were prepared for light microscopic (H&E and Masson's trichrome) and electron microscopic examination. Statistical analysis for the mean area % of collagen fibers was performed.

### Results

The results revealed that a low dose of paracetamol exerted no harmful effect on the histological structure of seminiferous tubules, whereas a high dose induced a mild harmful effect (few spermatogenic cells with cytoplasmic vacuolization and small dark nuclei) after 1 week that became moderate in the second week sections. The effect of paracetamol was severe in the third week sections, with cell loss and alteration of the basement membrane of some spermatogenic cells. Statistical analysis of collagen fibers revealed a significant increase in collagen fibers’ accumulation in the second and third week sections of the high-dose paracetamol group.

### Conclusion

It could be concluded that paracetamol is toxic to the rabbit testis when it is used in high repeated therapeutic doses. Thus, it should be used with caution, especially when a large, prolonged dose is indicated.

### Keywords:

high dose, paracetamol, seminiferous tubules

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**Introduction**

Paracetamol (known as acetaminophen in the United States) is a synthetic, nonopioid, centrally acting analgesic and antipyretic agent. Its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center [1].

It is recommended as a first-line therapy for pain associated with osteoarthrosis. Although discovered more than 100 years ago and in use extensively for 50 years, its mode of action is still unclear. The analgesic and antipyretic actions of acetaminophen resemble those of NSAIDs. However, it is commonly reported that paracetamol acts centrally and is at best a weak inhibitor of prostaglandin synthesis by cyclooxygenase [2].

Paracetamol is used in many forms either alone or in combination with other drugs (usually opiates) for analgesia and in other mixtures such as cold ‘cures’ for its analgesic and antipyretic properties [3].

It is a commonly used analgesic and antipyretic agent, and it is one of the most common causes of poisoning worldwide [4]. Its poisoning can be due to ingestion of excessive repeated or too-frequent doses. Repeated supratherapeutic ingestion is a significant clinical problem [5].

Paracetamol at therapeutic doses is rapidly metabolized in the liver principally through glucuronidation and sulfation, and only a small portion is oxidized by cytochrome P450. The precise mechanisms of paracetamol-induced toxicity
are not clear. The general consensus is that drug oxidation by various cytochrome P450s generates a highly reactive and cytotoxic intermediate, N-acetyl-p-benzoquinone imine (NAPQI), which conjugates with glutathione (GSH), causing the depletion of cellular GSH pools and an increase in oxidative stress and subsequently causing protein binding as a critical event in the toxicity [6,7]. The resulting oxidative stress in the cell may ultimately lead to cell death. NAPQI also binds to cell macromolecules, which can cause cell death [8]. Chronic ethanol intake, enzyme-inducing drugs, and malnutrition are thought to increase susceptibility to paracetamol toxicity due to depletion of intracellular GSH and greater accumulation of toxic metabolites [9].

The testis produces mature gametes through a complex process of stem germ cell proliferation to differentiation, modulated by a network of endocrine and paracrine regulatory inputs. The human testis is a known target organ for injury resulting from exposure to both therapeutic and toxic environmental agents. There are many possible mechanisms and manifestations of toxic damage to spermatogenesis. Within the testis, the three main target cells for toxicants that disrupt spermatogenesis are Leydig and Sertoli cells and the germ cells themselves [10].

Aim of the work
This study was conducted to determine the effect of paracetamol on the seminiferous tubule structures of adult rabbit.

Materials and methods
In this study, 18 adult male rabbits were utilized, with an average weight of 2000–2500 g each. Rabbits were housed in special cages, maintained under standard laboratory conditions, and fed ad libitum with available tap water. Paracetamol tablets 500 mg (El-Nasr Pharmaceutical Chemicals Co, Cairo, Egypt) were dissolved in normal saline and administered orally (through an orogastric tube). Two therapeutic doses of paracetamol were calculated and administered; the lowest was 8 mg/kg/day and the highest was 16 mg/kg/day for rabbits [11].

Rabbits were divided equally into three groups (n=6): a control group (group I), a low therapeutic dose group (group II), which received a daily oral dose of paracetamol (8 mg/kg/day) for 3 weeks, and a high therapeutic dose group (group III), which received a daily oral dose of paracetamol (16 mg/kg/day) for 3 weeks. Vascular perfusion fixation through the left ventricle with 1% glutaraldehyde was performed. Testicular specimens were obtained 1, 2, and 3 weeks from the start of the experiment and sections were prepared for light microscopic examination, H&E [12], and Masson’s trichrome [13] staining. For electron microscopic preparation, testis specimens were processed and ultrathin sections were prepared [14] in Tanta EM unit.

The mean area % for collagen fibers was measured in 10 Masson’s trichrome images for the first, second, and third week sections of each group using Image-Pro Plus program version 6.0 (Media Cybernetics Inc. Bethesda, Maryland, USA).

Statistics
All data were expressed as the mean of area percentage. Differences between groups were compared using an F-test with P < 0.05 considered as the level of statistical significance. The statistical analysis was carried out using Microsoft excel 2010 (Microsoft Egypt, Smart Village, Cairo, Egypt).

Results
Light microscope study
H&E stain
In the control group (group I), sections showed a normal histological pattern with seminiferous tubules and a narrow interstitium in between them. The seminiferous tubules were lined by several layers of spermatogenic cells, spermatogonia, and primary spermatocytes spermatids, separated by Sertoli cells. Many spermatozoa appeared in the tubular lumen (Fig. 1). Spermatogonia (dark and pale) appeared as rounded cells with rounded nuclei resting on a thin, straight basement membrane. Primary spermatocytes appeared as rounded cells with large rounded nuclei. Sertoli cells were found between spermatogenic cells with a pale cytoplasm and oval intended nuclei. Many flat myoid cells were observed around the basement membrane of each seminiferous tubule (Fig. 2). In the low-dose paracetamol group (group II), normal seminiferous tubules were seen in all sections (Fig. 3). In the high-dose paracetamol group (group III), a few spermatogenic cells appeared with small dark nuclei and a vacuolated cytoplasm in the first week sections (Figs 4 and 5). In the second week sections, spermatogenic cells with cytoplasmic vacuolization and pyknotic nuclei increased (Figs 6 and 7), which became severe in the third week sections (Fig. 8) with cell loss and alteration in the basement membrane in some areas and disorganization of spermatogenic cells (Fig. 9).

Masson’s trichrome stain
In the control group, sections of the testis showed delicate collagen fibers between the seminiferous tubules (Fig. 10). In the low-dose paracetamol group, sections showed a minimal increase in collagen fibers between the seminiferous tubules only in the third week sections (Fig. 11). In the high-dose paracetamol group, sections showed mild collagen fiber accumulation between the seminiferous tubules (Fig. 12) that became moderate in the second week sections (Fig. 13) and became severe in the third week sections (Fig. 14).

Statistical analysis
The mean area % for collagen fiber accumulation in the first, second, and third week sections of each group are represented, respectively, in Tables 1–3 and Histograms 1–3. There was a significant increase in collagen fiber accumulation in the second and third week sections and...
a nonsignificant increase in the first week sections of the high-dose paracetamol group (group III) compared with the control group.

**Electron microscopic study**

In the control group, sections showed spermatogonia and Sertoli cells lying on a thin, straight basement membrane, primary spermatocytes with large rounded nuclei (Fig. 15), spermatids with acrozoal vesicles, and spermatozoa (Fig. 16). The spermatogonium contained ovoid nuclei with mitochondria, free ribosomes, and rough endoplasmic reticulum in their cytoplasm. The intercellular space was narrow (Fig. 17). The Sertoli cell showed a large intended nucleus with a prominent nucleolus and peripheral mitochondria (Fig. 18). In the low-dose paracetamol group, normal testicular cell structures were seen similar to the control group (Fig. 19). In the high-dose paracetamol group, mild vacuolization in spermatogonia cells with a narrow intercellular space was seen (Fig. 20). Moderate cytoplasmic vacuolation with widening of the intercellular space and wavy basement membrane was found (Fig. 21) in the second week sections. In the third week sections, marked vacuolization, widening of the intercellular space with multiple fibroblast cells, and alteration of the basement membrane in certain areas were observed (Fig. 22).

**Figure 1.**

A photomicrograph of a section in the testis of the control group (group I) showing normal seminiferous tubules (S) lined by several layers of spermatogenic cells, spermatogonia (SG), primary spermatocytes (SR), spermatids (ST), separated by Sertoli cells (SE) with a narrow interstitium (I) in between. Many spermatozoa (SZ) in the tubular lumen can be seen. H&E, × 400.

**Figure 2.**

A higher magnification image showing spermatogonia; dark (SGD), light (SGL) resting on a thin, straight basement membrane (double arrows), primary spermatocytes (SR), Sertoli cells (SE) with a pale cytoplasm and oval intended nuclei (white arrow) and flat myoid cells (MY) around the basement membrane of each seminiferous tubule. H&E, × 1000.

**Figure 3.**

A photomicrograph of the third week section in the testis of the low-dose paracetamol group (group II) showing normal seminiferous tubules (S); spermatogenic cells (SP) separated by Sertoli cells (SE) with a narrow interstitium (I) in between. H&E, × 400.

**Figure 4.**

A photomicrograph of the first week section in the testis of can be seen high-dose paracetamol group (group III) showing few spermatogenic cells (SP) with small condensed nuclei and a vacuolated cytoplasm (V). Sertoli cells (SE) can be seen. H&E, × 400.
Figure 5.

A higher magnification image showing cytoplasmic vacuolization (V) of some spermatogenic cells (SP). Sertoli cells (SE) with oval intended nuclei and flat myoid cells (MY) around the basement membrane (double arrows) of each seminiferous tubule can be seen. H&E, ×1000.

Figure 6.

A photomicrograph of the second week section in the testis of the high-dose paracetamol group (group III) showing many spermatogenic cells with a vacuolated cytoplasm (V), small dark nuclei (arrow head), and slight widening of the interstitium (I), (S) seminiferous tubule. H&E, ×400.

Figure 7.

A higher magnification image showing cytoplasmic vacuolization (V) and small dark nuclei (arrow head) of many spermatogenic cells (SP), Sertoli cells (SE), and flat myoid cells (MY) with alteration in the basement membrane (double arrows) in some areas of the seminiferous tubules. Areas of cell loss (AR) can be seen. H&E, ×1000.

Figure 8.

A photomicrograph of the third week section in the testis of the high-dose paracetamol group (group III) showing marked cytoplasmic vacuolization (V), small dark nuclei (arrow head) of many spermatogenic cells, and widening of the interstitium (I), seminiferous tubule (S), thin irregular basement membrane (double arrow) is noticed. H&E, ×400.

Figure 9.

A higher magnification image showing marked cytoplasmic vacuolization (V) and small dark nuclei (arrow head) of many spermatogenic cells (SP), Sertoli cells (SE), and flat myoid cells (MY) with alteration in the basement membrane (double arrows) in some areas of the seminiferous tubules. Areas of cell loss (AR) can be seen. H&E, ×1000.

Figure 10.

A photomicrograph of a section in the testis of the control group (group I) showing a thin straight basement membrane around the seminiferous tubules with delicate collagen fibers (black arrow) between them. Masson’s trichrome, ×400.
Figure 11. A photomicrograph of the third week section in the testis of the low-dose paracetamol group (group II) showing minimal accumulation of collagen fibers (black arrow) between seminiferous tubules. 
Masson's trichrome, × 400.

Figure 12. A photomicrograph of the first week section in the testis of the high-dose paracetamol group (group III) showing mild accumulation of collagen fibers (black arrow) between seminiferous tubules. 
Masson's trichrome, × 400.

Figure 13. A photomicrograph of the second week section in the testis of the high-dose paracetamol group (group III) showing moderate accumulation of collagen fibers (black arrow) between seminiferous tubules. 
Masson's trichrome, × 400.

Figure 14. A photomicrograph of the third week section in the testis of the high-dose paracetamol group (group III) showing marked accumulation of collagen fibers (black arrow) between seminiferous tubules. 
Masson's trichrome, × 400.

Figure 15. An electron micrograph of a section in testis of the control group (group I) showing spermatogonia cells (SG) lying on a thin, straight basement membrane (double arrows) and Sertoli cell (SE) with a large indented nucleus (arrow). 
Primary spermatocyte (SR) can be seen. EM, × 3000.

Figure 16. An electron micrograph of a section in testis of the control group (group I) showing spermatids (ST); some have acrosomal vesicles (AV) and spermatozoa (SZ). 
EM, × 4000.
Figure 17. An electron micrograph of a section in testis of the control group (group I) showing spermatogonium cell with a large ovoid nucleus (N) and an apparent nucleolus (NU), mitochondria (M), endoplasmic reticulum (ER), and free ribosomes (R). Narrow intercellular space (IC) can be seen.

EM, × 6000.

Figure 18. An electron micrograph of a section in testis of the control group (group I) showing Sertoli cell (SE) with large indented (arrow) nucleus (N) and prominent nucleolus (NU) and peripheral mitochondria (M). The basement membrane (double arrows) appeared thin and straight.

EM, × 6000.

Figure 19. An electron micrograph of the 3rd week sections in the testis of low dose paracetamol group (group II) showing spermatogonium cells (SG) with electron dense nuclei lying on thin, straight basement membrane (double arrows) and Sertoli cell (SE). Myoid cell (MY) is noticed.

EM, × 3000.

Figure 20. An electron micrograph of the 1st week section in the testis of high dose paracetamol group (group III) showing vacuolization (V) of spermatogonum cell (SG) cytoplasm. The basement membrane (double arrows) appeared clear and straight.

EM, × 3000.

Figure 21. An electron micrograph of the 2nd week section in the testis of high dose paracetamol group (group III) showing moderate vacuolization (V) of spermatogonia cells (SG) with widening of the intercellular space (IC) and the basement membrane (double arrows) appears wavy.

EM, × 3000.
Figure 22.

An electron micrograph of the third week sections in the testis of the high-dose paracetamol group (group III) showing disorganized spermatogonia cells (SG) with a vacuolated cytoplasm (V), widening of the intercellular space (IC), disruption of the basement membrane (double arrows) in certain areas, and myoid (MY) cells with large flat nuclei. Multiple fibroblasts (Fi) can be seen.

EM, × 6000.

Histogram 1.

Histogram 2.

Histogram 3.

Table 1. Mean area % of collagen fibers, SD, and P-value in group II and group III in first week sections compared with the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean area %</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>SD±</td>
<td>0.005</td>
<td>0.009</td>
<td>0.010</td>
</tr>
<tr>
<td>P-value</td>
<td>0.14</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

S, significant.

Table 2. Mean area % of collagen fibers, SD, and P-value in group II and group III in second week sections compared with the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean area %</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>SD±</td>
<td>0.006</td>
<td>0.009</td>
<td>0.018</td>
</tr>
<tr>
<td>P-value</td>
<td>0.8546</td>
<td>0.0009</td>
<td></td>
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<tr>
<td>Significance</td>
<td>NS</td>
<td>S</td>
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</tbody>
</table>

S, significant.

Table 3. Mean area % of collagen fibers, SD, and P-value in group II and group III in third week sections compared with the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean area %</td>
<td>1</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>SD±</td>
<td>0.005</td>
<td>0.007</td>
<td>0.021</td>
</tr>
<tr>
<td>P-value</td>
<td>0.2755</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>S</td>
<td></td>
</tr>
</tbody>
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S, significant.

Discussion

Paracetamol is an effective, mild analgesic, antipyretic agent and is probably the most widely used of all drugs in the world. In many countries, it is fashionable to misuse over-the-counter analgesics for self-poisoning [15]. As a result, paracetamol has become a victim of its own success [16].

Paracetamol is widely used in Egypt, especially since the spread of swine flu. As the testis undergoes constant division and cell differentiation, which makes it more vulnerable to toxic substances as this tissue is of great importance for reproduction, this study was conducted to...
determine the effect of paracetamol on the seminiferous tubules of rabbit testis.

Paracetamol was administered orally in mice at two therapeutic doses: low (40 mg/kg/day) and high (80 mg/kg/day) [17]. In the present study, the doses were calculated according to Paget’s formula [11].

In the present study, when paracetamol was administered at a small dose (group II), it had no harmful effect on the histological structure of seminiferous tubules, except minimal (nonsignificant) collagen fiber accumulation after 3 weeks as seen on Masson’s trichrome stain. This was in agreement with the result of some authors [18], who reported that in low doses, paracetamol is believed to be safe. These results were explained by others [19,20], who stated that the toxicity of paracetamol is not produced by the parent compound but is mediated by cytochrome P450 metabolism to the reactive NAPQI and, at low doses, this metabolite is detoxified by GSH. In contrast, some researchers [17] reported that spermatogenic cell alterations occurred in testis treated with a low dose of paracetamol.

In the present study, paracetamol at a high dose (group III) exerted a mild effect on seminiferous tubule structure: cytoplasmic vacuolization and nonsignificant collagen fiber accumulation in the first week sections that became moderate in the second week, with significant collagen fiber accumulation. Severe harmful effects such as marked cytoplasmic vacuolization, small dark nuclei, significant collagen fiber accumulation between seminiferous tubules, widening of the intercellular space with multiple fibroblasts (which led to an increase in collagen fiber accumulation), cell loss, and basement membrane alteration, were seen in the third week sections. This was in agreement with researchers [21] who reported that paracetamol is toxic at higher doses and others [22] who reported that testicular lesions were only detected in a high-dose acetaminophen (paracetamol) group. Also, some researchers [23] reported that a high dose of paracetamol in mice led to alterations in the relative proportion of individual testicular cell types. In contrast, some authors [24] reported that there no significant histopathological changes were observed in organs of the higher dose level paracetamol-treated groups of male rats compared with the control group and they attributed the negative toxic effect of paracetamol to its different route of administration (intravenous infusion). Some scientists [17,18] have described the testicular histological changes caused by a high dose of paracetamol. They reported that light microscope analysis showed that the animals treated with paracetamol had some deformed seminiferous tubules, with a separation of the basal cells. Less frequently, tubules were found to show total degeneration, surrounded by fibrous interstitial tissue. With electron microscopy, loss of contact between cells was observed. Lacunae were occasionally found between cells.

In the present study, the harmful effect of a high dose of paracetamol increased with the prolonged duration of use of the drug. This was in agreement with researchers [3] who reported that injury caused by acetaminophen (paracetamol) is apparent at presentation and related to the magnitude and duration of the dose. In contrast, others [22] have reported that degeneration of seminiferous tubules of the testes after acetaminophen exposure persisted throughout the rest of the study without significant change in severity.

In the present study, Sertoli cells were not affected by administration of paracetamol in all sections, even in the high-dose group. This was in agreement with researchers [22] who reported that Sertoli and interstitial cells showed no visible changes after high-dose acetaminophen exposure.

The mechanism of paracetamol testis toxicity has been attributed by some scientists [25] to paracetamol-metabolizing enzyme activity found in the testis; however, compared with the liver, the relative level of P450 versus GSH transferase and GSH is low in the testis. Therefore, it is not likely that reactive metabolites formed in the liver are transported to the testicular cells. In accordance with this principle, it was found that exposure to paracetamol caused neither a depletion of GSH (nonprotein sulfydryls) in the testis nor a marked increase in covalent binding. Thus, one should consider the possibility that testicular toxicity was induced by a mechanism different from the formation of a reactive metabolite. Spermatogonia and primary spermatocytes do not P450 enzymes or peroxidases. Thus, most probably unmetabolized paracetamol interferes with testicular cell DNA synthesis, likely by the inhibition of ribonucleotide reductase, leading to a reduction in the normal deoxyribonucleotide of spermatogonia and spermatocytes. Paracetamol may also cause cell death (apoptosis) through inhibition of DNA replication.

Paracetamol has been found to be a highly specific dose-dependent inhibitor of DNA synthesis in testicular tissue [26]. Peroxynitrite, which is formed by a reaction between superoxide and nitric oxide and can damage protein, DNA, and lipids, has been suggested to be a critical mediator of paracetamol-related organ toxicity [27]. Cyclophilin A (CypA) is a mediator of sepsis. Its effect was mediated through the extracellular CypA receptor. As CypA is an abundant intracellular protein, it is likely to be released from cells injured by paracetamol [28].

It can be concluded that paracetamol is harmful to the testis when consumed in large repeated doses. Thus, it should be used with caution, especially when a large and prolonged dose is indicated.

Acknowledgements

Conflicts of interest

There is no conflict of interest to declare.

References

دراسة هستولوجية لتأثير عقار الباراسيتامول على الأنيببات المنوية فى الأرانب البالغة
(دراسة بالميكروسكوب الضوئى والإلكترونى)

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قسم السموم الطبية – كلية طب بنها

عقار الباراسيتامول (أسيتامينوفي) يستخدم على نطاق واسع كمسكن و خافض للحرارة كما انه متاح دون وصفة طبية. وقد وجد أن استخدامه بجرعات عالية يسبب أضرارا خاصية بالكبد.

تهدف هذه الدراسة إلى تقييم تأثير عقار الباراسيتامول على الأنيببات المنوية في الأرانب البالغة.

تضمنت الدراسة 18 أرنب ذكر بالغ، قسمت بالتساوي إلى ثلاث مجموعات. المجموعة الأولى استخدمت كمجموعة تضمنت 18 أرنب، المجموعة الثانية كانت مجموعة جرعة الباراسيتامول العلاجية الصغيرة (8 مجم/كجم من وزن الأرنب يوميا بالفم) و المجموعة الثالثة كانت مجموعة جرعة الباراسيتامول العلاجية الكبيرة (16 مجم/كجم من وزن الأرنب يوميا بالفم).

أخذت العينات من الخصية من الأرانب بالفم أسبوعيًا و أعدت للفحص بالميكروسكوب الضوئى (صبغات الهيماتوكسيلين والأيوسين - ماسون ثلاثي اللون) والميكروسكوب الإلكتروني. المسبحة المؤية لمساحة الياف الكولاجين تم قياسها في صور صبغة الماسون ثلاثي اللون لكل مجموعة و تم تحليل النتائج إحصائيا.

كشفت النتائج أن الجرعة العلاجية الصغيرة من عقار الباراسيتامول ليس لها تأثير ضار على التركيب النسيجي للأنيببات المنوية بينما الجرعات العلاجية الكبيرة كان لها تأثير ضار واضح. و كان هذا التأثير ضعيف نسبيا بعد أسبوع واحد من إعطاء العقار (فجوات بسيطة بالسيتوبلازم و أنوية صغيرة داكنة) بينما كان هذا التأثير متوسطا في عينات الأسبوع الثاني و شديدًا في عينات الأسبوع الثالث. صب وخج عينات الأسبوع الثالث مصحوبا بفقدان بعض الخلايا النطفية مع تغيرات في الغشاء الفاعل. التحليل الإحصائي لجمع ألياف الكولاجين كشف عن وجود زيادة كبيرة مؤثرة لجمع ألياف الكولاجين في عينات الأسبوع الثاني و الثالث لمجموعة جرعة الباراسيتامول العلاجية الكبيرة.

هذه النتائج توضح أن عقار الباراسيتامول له تأثير سام على نسيج خصية ذكور الأرانب البالغة عندما يستخدم بجرعات علاجية كبيرة و متكررة وذلك يمنح بالحرص عند استخدامه خاصة عندما يوصف بجرعات كبيرة و لمدة طويلة.

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