Comparison of the intensity of oxidative stress during chemotherapy alone and chemotherapy combined with antioxidant therapy in spontaneous mammary tumours in dogs

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SUMMARY
As many anti-tumour drugs exert their cytotoxic effect via free radical-mediated mechanisms, the combined administration of antioxidants would alleviate side effects of the chemotherapy. The aim of this study was to evaluate the oxidant and antioxidant status of dogs with mammary adenocarcinomas after surgical removal of the tumours treated with chemotherapy (epirubicin and cyclophosphamide) alone (group I, n = 7) or coupled to antioxidant (vitamins E and C) supplementation (group II, n = 7) by monitoring the serum malondialdehyde (MDA), tocopherol and ascorbate concentrations and the catalase (CAT) activity in serum as well as the reduced glutathione (GSH) and superoxide dismutase activity in erythrocytes according to time. The co-administration of antioxidant vitamins with chemotherapeutic drugs markedly depressed the production of blood lipid peroxidation products (MDA). In parallel, the erythrocyte antioxidants were recruited (GSH concentrations declined and SOD activities increased) while serum antioxidants remained constant (vitamin C) or decreased (vitamin E) during the chemotherapy duration. Fifteen days after the end of treatment, the serum vitamin C concentrations become significantly higher in dogs supplemented with antioxidant vitamins whereas the serum vitamin E concentrations still remained depressed. These results suggest that the associated antioxidant treatment decreased the oxidative stress intensity by promoting the mobilisation of tissue antioxidant systems and exchanges with the blood store.

Keywords: Dog, mammary adenocarcinoma, epirubicin, cyclophosphamide, oxidative stress, antioxidants, glutathione, vitamins, superoxide dismutase.

RÉSUMÉ
Comparaison de l'intensité du stress oxydatif lors d’une chimiothérapie seule ou associée à un traitement antioxydant dans les tumeurs mammaires canines spontanées

Comme beaucoup d’agents anticancéreux exercent leur action cytotoxique par des mécanismes radicaux, il est probable qu’une administration conjointe d’antioxydants puisse diminuer les effets secondaires d’une chimiothérapie. L’objectif de cette étude a été d’évaluer les statuts oxydants et antioxydants des chiens présentant des adénocarcinomes mammaires traités, après exérèse des tumeurs, soit par chimiothérapie (épirubicine et cyclophosphamide) seule (groupe I, n = 7), soit par chimiothérapie couplée à une supplémentation en vitamines anti-oxydantes C et E (groupe II, n = 7) en suivant au cours du temps les concentrations en malondialdéhyde (MDA), en tocophérols et en ascorbate et l’activité de la catalase (CAT) dans le sérum ainsi que la concentration de glutathion réduit (GSH) et l’activité de la superoxyde dismutase (SOD) dans les érythrocytes. L’administration conjointe d’antioxydants et d’agents anticancéreux a permis de nettement diminuer la quantité circulante de produits issus de la peroxidation lipidique (MDA). Parallèlement, les antioxydants intra-érythrocytaires ont été recrutés (diminution des concentrations de GSH et augmentation de l’activité SOD) tandis que les antioxydants sériques sont restés constants (vitamine C) ou ont diminué (vitamine E) durant la durée de la chimiothérapie. Quinze jours après la fin du traitement, les concentrations sériques en vitamine C sont devenues significativement plus élevées chez les chiens supplémentés alors que celles en vitamine E sont restées encore faibles. Ces résultats suggèrent qu’un traitement antioxydant associé à la chimiothérapie diminue l’intensité du stress oxydatif en promouvant l’utilisation des systèmes antioxydants tissulaires ainsi que les échanges avec le stock antioxydant sanguin.

Mots clés : Chien, adénocarcinome mammaire, épirubicine, cyclophosphamide, stress oxydatif, antioxydants, glutathion, vitamines, superoxyde dismutase.

Introduction
During the last years, the interest towards reactive oxygen species (ROS) [superoxide radical (O2·-)], hydrogen peroxide (H2O2) and hydroxyl radical (OH·)] is continuously increasing after demonstration of their essential role in the pathogenesis of many diseases, including malignancies [12, 22, 24, 26, 31].

According to a number of experimental data, some anticancer drugs such as doxorubicin, bleomycin, vincristin, cyclophosphamide and hydroxyurea exert their cytotoxic effect by free radicals-mediated mechanisms [16, 30]. The anthracyclines undergo a one-electron reduction to semiquinone free radicals which are rapidly oxidized in the presence of oxygen, generating the superoxide ion and then H2O2 and OH· [4, 34]. The other ROS generated by the cascade of free radicals are believed to be the main cause for anthracycline-induced peroxidation damage of membrane lipids and DNA [18, 28].

Cyclophosphamide is a DNA alkylating anticancer drug that requires a metabolic activation. It could be oxidized by
a number of peroxidases, including 15-lipoxygenase [21]. This reaction is significantly inhibited in the presence of antioxidants that presume the involvement of free-radical mechanisms in the drug effect [21].

The interest of the antioxidant co-administration with cytotoxic drugs has been extensively disputed. There are numerous theories about the interaction of antioxidants and antineoplastic drugs that are contradictory and require extensive research in both human and animal patients [37, 39, 42]. Up to now, there is only one report about the intake of dietary antioxidants as adjuvant therapy to chemotherapy with drugs with free-radical-mediated mechanism of action [25], but data about the outcome of the combined therapy with chemotherapeutic drugs and antioxidants in bitches with spontaneous mammary neoplasms are not available.

The purpose of this study was to evaluate the oxidant / antioxidant balance in bitches with spontaneous mammary adenocarcinomas, treated either with chemotherapy alone or with chemotherapy combined with antioxidants by determination of the serum malondialdehyde (MDA), vitamin C and vitamin E concentrations, the erythrocyte reduced glutathione (GSH) content and the serum catalase activity (CAT).

**Materials and Methods**

**ANIMALS AND TREATMENTS**

The study was performed in 14 bitches, 6 to 14 years old, weighing from 4 to 29 kg, divided into two groups of 7 dogs each. The breed distribution of dogs was as followed: 6 Bolognese, 1 Mittelschnauzer, 1 German shepherd, 1 Dachshund, 1 Miniature Pinscher, 1 Afghan hound, 1 Setter and 2 mixed-breeds. In all dogs, a mammary adenocarcinoma was confirmed by histopathology.

In the first group, the therapy consisted in surgical removal of the tumour and chemotherapy, whereas in the second group the surgical removal of the tumour was completed by chemotherapy associated with antioxidant therapy. The chemotherapeutic protocol in both groups was identical. It started ten days after the surgery with epirubicin (Farmorubicin®, Pharmacia & Upjohn, Milan, Italy) and cyclophosphamide (Endoxan®, Asta Medica, Frankfurt) as followed: i) intravenous injection of epirubicin at a dose of 20-30 mg/m² once weekly, for 3 consecutive weeks and ii) intravenous injection of cyclophosphamide at a dose of 80-100 mg/m², once weekly, for 3 consecutive weeks. During the entire course of the chemotherapy, the dogs from the second group received vitamin C (daily sub-cutaneous dose of 50 mg/kg) and vitamin (weekly intramuscular dose 30 000 UI/kg) as antioxidants.

**BLOOD ANALYSIS**

All blood analyses were carried out at the following intervals: prior to the surgery (period 1); 10 days after the surgery at the first chemotherapy (period 2); 17 days after the surgery when epirubicin was injected for the second time (period 3); 42 days after the surgery, i.e. 15 days after the last injection of cyclophosphamide (period 5). Blood samples were collected by puncture of the cephalic antebrachial vein into sterile tubes without anticoagulant for serum collection and in tubes with K3-EDTA as anticoagulant for erythrocyte preparation. After clotting at room temperature for one hour, samples were centrifuged at 1 000 g, at 4°C for 10 minutes and sera were carefully harvested and stored at -20°C until analysis. Blood samples with anticoagulant were immediately centrifuged at 1 000 g, at 4°C for 10 minutes and blood plasma was harvested. The erythrocyte pellet was washed three times with saline, then was suspended again in 4 volumes ice-cold distilled water and left for 5 min at 4°C to lyse the erythrocytes.

The lipid peroxidation assay (TBARS determination) is based on the formation of a 1:2 red adduct between malondialdehyde (MDA) and 2-thiobarbituric acid in acid medium whose the absorbance was measured at 532 nm after extraction with n-butanol [2, 40]. As a MDA standard, 1,1,3,3 tetraethoxypropane (Sigma Aldrich Chemie GmbH, Munich, Germany) was used.

Serum catalase (CAT) activities were assayed by the method of Goth [14] based on the formation of stable yellow complex between the substrate (hydrogen peroxide in sodium-potassium phosphate buffer, pH 7.4) and ammonium molybdate, quantified at 405 nm.

Serum tocopherols (vitamin E) was determined by the method of QUAFE et al. [32] based on the Emmerie-Engel colour reaction with ferric chloride and 2,2'-dipyridyl to give a red coloured compound that was further quantified at 520 nm against a set of standard solutions in ethanol.

Serum ascorbic acid (vitamin C) concentrations were quantified after protein precipitation with 10% trichloro-acetic acid. The assay is based on the reduction of ferric chloride by ascorbic acid, the resulting ferrous ion forming with the 2,4,6-tripyridyl-s-triazine a purple coloured compound for which the absorbance was maximal at 595 nm in a high molarity acetic buffer [10].

The erythrocyte superoxide dismutase activity (U/mg Hb) was assayed with a commercial kit (Superoxide Dismutase Kit, cat. N° 7500-100-K, R & D Systems, UK).

Reduced glutathione is determined on the basis of its reaction with 5,5-dithiobis 2-nitrobenzoic acid (DTNB) to give a stable yellow coloured complex [5]. The absorbance, measured at 412 nm along with standard (L-glutathione, Sigma Aldrich) and a blank, is directly proportional to the serum GSH concentration.

**STATISTICAL ANALYSIS**

The statistical analysis was performed with the non-parametric Friedman’s test for two-way repeated measures analysis. In case of significant P-values (P < 0.05), the non-parametric Tukey HSD test was then applied. Correlation coefficients among assayed parameters were calculated by the Pearson's correlation test.
Results

The oxidant and antioxidant status of both groups of bitches (group I: surgery and chemotherapy; group II: surgery, chemotherapy and antioxidant therapy) at the different experimental periods are presented in Table I.

The erythrocyte GSH and serum vitamin C concentrations greatly fluctuated according to time in both groups. By contrast, the serum MDA concentrations tended to gradually decline in the 2 groups but differences with baseline (pre-surgery) values were not statistically significant. In the same way, the erythrocyte superoxide dismutase (SOD) activity progressively and significantly declined in the group I (treated by surgery and chemotherapy alone): values recorded for the 2nd and the 4th experimental periods (between surgery and the first epirubicin injection and between the 2nd and the 3rd epirubicin injections, respectively) were significantly reduced ($P < 0.05$) compared to baseline values and minimum activities were observed for the 3rd period (between the 1st and the 2nd epirubicin injections) (vs. baseline values: $P < 0.01$). The erythrocyte SOD activities also tended to gradually decrease for reaching minimum values at the 4th period but differences with initial values were not significant. The serum vitamin E concentrations exhibited relatively great variations according to time in the group I: high values were mainly recorded during the 2nd and 5th periods, the difference with pre-surgery values being significant only 15 days after cessation of the therapy ($P < 0.05$). On the contrary, when dogs were submitted to chemotherapy combined with anti-oxidant administration, this parameter tended to decrease just after surgery (period 2) then remained relatively constant.

The serum MDA concentrations were significantly more elevated in the group I (surgery and chemotherapy alone) than in the group II (surgery plus chemotherapy combined with antioxidants) at the 2nd ($P < 0.05$), the 3rd and the 4th experimental periods ($P < 0.01$), i.e. after surgery to the last epirubicin injection. On the other hand, some antioxidant (GSH and vitamin E) concentrations were also significantly increased in the group I compared to the group II from the first to the third epirubicin administration (periods 3 and 4: $P < 0.01$) for the GSH concentrations and from surgery to 15 days after the last anticancer drug injection (periods 2 and 4: $P < 0.05$ and periods 3 and 5: $P < 0.01$) for the total toco-pherol concentrations. In parallel, significant reductions of the serum vitamin C concentrations and of the erythrocyte SOD activities were observed in the dogs receiving chemotherapy alone compared to dogs receiving chemotherapy associated to antioxidant treatment at the 5th period ($P < 0.01$) and at the 3rd period ($P < 0.05$) respectively.

As far as the serum catalase (CAT) activities were concerned, no time effect and no group effect were evidenced because of the great value dispersion.

In the first experimental group, there was a statistically significant positive correlation between GSH content and serum vitamin C concentrations (0.342, $P < 0.05$) as well as a negative relationship between GSH and vitamin E (-0.348, $P < 0.05$). In the group supplemented with antioxidants, serum MDA levels correlated positively with SOD activities (0.353, $P < 0.05$), whereas GSH was proportional to vitamin E concentrations (0.352, $P < 0.05$). There were no statistically significant correlations among the other tested biochemical parameters in both groups.

Discussion

It is reported that cancer patients treated by Adriamycin, mitomycin C, bleomycin are suffering from an oxidative stress because of the drug-induced free radical production [30].

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
\text{Parameters} & \text{Period 1} & \text{Period 2} & \text{Period 3} & \text{Period 4} & \text{Period 5} \\
\hline
\text{MDA (µmol/L)} & \text{Group I: 14.9 (12.1-31.7)} & \text{17.0 (11.9-25.7)} & 16.3 (11.4-31.8) & 13.2 (11.3-32.8) & 10.2 (8.0-33.4) \\
& \text{Group II: 14.3 (8.8-15.5)} & 14.6 (10.8-19.1) & 10.3 (5.3-16.3) & 10.7 (5.9-13.0) & 9.2 (7.5-12.0) \\
\hline
\text{CAT (kU/L)} & \text{Group I: 17 (15-43)} & 32 (12-80) & 20 (6-35) & 22 (8-92) & 29 (5-70) \\
& \text{Group II: 24 (11-77)} & 18 (12-27) & 18 (8-55) & 23 (10-48) & 23 (9-98) \\
\hline
\text{GSH (µmol/L)} & \text{Group I: 0.62 (0.40-1.37)} & 0.52 (0.38-0.86) & 0.83 (0.57-0.98) & 0.96 (0.52-1.35) & 0.63 (0.48-0.79) \\
& \text{Group II: 0.50 (0.33-1.03)} & 0.61 (0.31-0.68) & 0.45 (0.31-0.64) & 0.36 (0.23-0.67) & 0.52 (0.44-0.76) \\
\hline
\text{Vit. E (µmol/L)} & \text{Group I: 43.1 (23.8-58.2)} & 60.1 (42.8-84.3) & 42.6 (40.0-69.5) & 48.0 (30.4-54.4) & 67.3 (43.9-73.7) \\
& \text{Group II: 47.7 (25.1-63.8)} & 28.9 (21.2-48.8) & 39.3 (21.2-49.1) & 34.0 (22.6-47.0) & 38.0 (27.8-49.0) \\
\hline
\text{SOD (µmol/L)} & \text{Group I: 43.1 (23.8-58.2)} & 60.1 (42.8-84.3) & 42.6 (40.0-69.5) & 48.0 (30.4-54.4) & 67.3 (43.9-73.7) \\
& \text{Group II: 47.7 (25.1-63.8)} & 28.9 (21.2-48.8) & 39.3 (21.2-49.1) & 34.0 (22.6-47.0) & 38.0 (27.8-49.0) \\
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\end{array}
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Vit.: vitamin; MDA: Malondialdehyde; CAT: Catalase; GSH: Glutathione; SOD: Superoxide dismutase

Different $ab$ superscripts indicate significant difference between the 2 groups for a given period ($P < 0.05$).

Different $AB$ superscripts indicate significant difference according to time for a given group ($P < 0.05$).

\[\text{Table I : Time course of oxidant and antioxidant status in dogs with spontaneous mammary tumours submitted to different treatment protocols (Group I, n = 7: surgery and chemotherapy; Group II, n = 7: surgery, chemotherapy + antioxidant therapy) at different periods (period 1: prior to surgery; period 2: between surgery and the first epirubicin injection; period 3: between the first and the second epirubicin injections; period 4: between the second and the third epirubicin injections; period 5: 15 days after the end of chemotherapy. Data are presented as median (and range).}\]
The redox cycle of anthracyclines supports the formation of free radicals that are believed to play an important role for their cardiotoxicity [17].

The application of antioxidants during the chemotherapy of cancer patients is intensively debated: according to some authors, antioxidants should not be administered because they decrease the efficiency of the anticancer drugs [15, 25, 39], whereas others believe that their cautious use could be beneficial in cancer therapy both independently or combined with chemotherapeutic drugs [1, 11, 36-38, 42]. For example, COULTER et al. [9] do not admit the efficiency of the antioxidant vitamins C and E for either prevention or treatment of neoplasms. In the same way, there is no consensus on the therapeutic doses of these vitamins.

FREI [13] has demonstrated the powerful antioxidant action of vitamin C (superior to all other biological plasma antioxidants) on lipids against various oxidative stress factors. The antioxidant effect of the ascorbic acid is related to its capacity to lose a hydrogen atom and to form a relatively stable ascorbate free radical. In excess of ROS, ascorbate could be effective against the superoxide radical, the hydrogen peroxide and the hydroxyl radical [35, 41]. Besides, this vitamin reduces the formation of hydroxyl free radicals from hydroperoxide during the Fenton reaction by reducing Fe3+ (which catalyses the Fenton reaction) into Fe2+ [29]. Although vitamin C is known to stimulate the immune system by inhibiting the nitrosamine formation and blocking the metabolic activation of carcinogens, its main preventing effects against cancer could be mainly related to its protection against the deleterious effects of an oxidative stress [29]. The tocopherols are highly effective in preventing the auto-oxidation of lipids and this is their essential role in biological tissues [8]. It was reported that the vitamin E therapy was found to have an important neuroprotective effect in chemotherapy-induced peripheral nerve damage [3]. In the same way, the vitamin E administration could protect normal cells from the cisplatin-induced oxidative damage, but could also reduce the effect of cisplatin on tumour cells [7].

In the present study, the serum MDA concentrations were significantly lower when chemotherapy was associated to an adjuvant antioxidant (vitamins C and E) treatment than when chemotherapy alone was performed, showing that the intensity of the oxidative stress was depressed in this case. Moreover, the diminution of the oxidative stress was coupled to the consumption of some endogenous antioxidant pools such as glutathione, since the erythrocyte GSH concentrations were significantly decreased mainly during the chemotherapy in dogs receiving chemotherapy and antioxidants compared to dogs receiving epirubicin and cyclophosphamide alone. In parallel, serum vitamin E concentrations were also markedly reduced during the whole chemotherapy period in these dogs (chemotherapy plus antioxidants) and the serum vitamin C concentrations were not significantly increased whereas these animals were supplemented with vitamins E and C. KAWAI et al. [23] reported that after vitamin E supplementation, serum α-tocopherol concentrations were reduced after physical exercise whereas the erythrocyte concentrations were maintained after exercise. The authors suggest that as erythrocytes suffer from oxidative stress during exercise, the local vitamin E pool is effectively consumed to protect them but it is rapidly restored from the circulating vitamin E pool, resulting in a steady erythrocyte α-tocopherol amount but decreased serum-α-tocopherol concentrations under oxidative stress. In the same way, the decrease of the serum tocopherol concentrations observed in the supplemented dogs may reflect some shifts of vitamin E from serum to oxidized cells whereas in dogs, not supplemented with vitamin E, tissue vitamin stores are probably mobilised leading to enhancement of the circulating vitamin E concentrations. As far as the ascorbic acid is concerned, it would be possible that similar exchange mechanisms between tissues and blood were involved but with a lower intensity, leading to heterogeneous fluctuations of this parameter according to time and the absence of a significant difference between the 2 groups during the whole chemotherapy period. It is only when the oxidative phenomena tend to be attenuated 15 days after the end of the chemotherapy that the serum vitamin C concen-

<table>
<thead>
<tr>
<th>GSH</th>
<th>Vit. E</th>
<th>Vit. C</th>
<th>SOD</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA</td>
<td>rI = -0.116, NS</td>
<td>rI = -0.164, NS</td>
<td>rI = -0.219, NS</td>
<td>rI = -0.026, NS</td>
</tr>
<tr>
<td></td>
<td>rII = 0.101, NS</td>
<td>rII = -0.105, NS</td>
<td>rII = -0.270, NS</td>
<td>rII = 0.353, P &lt; 0.05</td>
</tr>
<tr>
<td>GSH</td>
<td>rI = -0.348, P &lt; 0.05</td>
<td>rI = 0.342, P &lt; 0.05</td>
<td>rI = 0.068, NS</td>
<td>rI = 0.234, NS</td>
</tr>
<tr>
<td></td>
<td>rII = 0.352, P &lt; 0.05</td>
<td>rII = 0.084, NS</td>
<td>rII = 0.263, NS</td>
<td>rII = 0.006, NS</td>
</tr>
<tr>
<td>Vit. E</td>
<td>rI = -0.025, NS</td>
<td>rI = -0.007, NS</td>
<td>rI = 0.234, NS</td>
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<tr>
<td></td>
<td>rII = -0.210, NS</td>
<td>rII = -0.271, NS</td>
<td>rII = -0.321, NS</td>
<td></td>
</tr>
<tr>
<td>Vit. C</td>
<td>rI = -0.171, NS</td>
<td>rI = -0.090, NS</td>
<td>rI = 0.092, NS</td>
<td></td>
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<tr>
<td></td>
<td>rII = -0.105, NS</td>
<td>rII = 0.262, NS</td>
<td></td>
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</tr>
</tbody>
</table>

rI: Correlations were calculated for the group I; rII: correlations were calculated for the group II; NS: not significant; MDA: Malondialdehyde; GSH: Glutathione; Vit.: vitamin; SOD: Superoxide dismutase; CAT: Catalase.

TABLE II: Correlations obtained between the biochemical markers of oxidant and antioxidant status in dogs treated with chemotherapy alone (group I) or coupled with antioxidant (vitamins E and C) supplementation (group II).
trations become significantly more elevated in the group of supplemented dogs, suggesting that in fact, endogenous vitamin C is globally spared.

On the other hand, the erythrocyte SOD activity was significantly increased in vitamin C and E supplemented dogs compared to not supplemented dogs between the 2 first injections of epirubicin, suggesting that erythrocytes submitted to the oxidative stress have reduced the superoxide anion into \( \text{H}_2\text{O}_2 \) with a better yield. In parallel, as the Fenton reaction later coupled to the oxygen dismutation was inhibited by ascorbate at least in vitro, the production of hydroxyl free radicals and consequently the oxidative stress intensity were limited but the hydrogen peroxide may accumulate. The catalase is an enzyme involved in the reduction of \( \text{H}_2\text{O}_2 \) and may alleviate this accumulation. Surprisingly, in the present study, the serum CAT activity was not significantly altered by the vitamin supplementation. Nevertheless, the CAT implication in the reduction of oxidative stress during chemotherapy combined with antioxidant treatment cannot be ruled out without the determination of the CAT activity in erythrocytes.

The group of dogs submitted to chemotherapy only exhibited a negative correlation between erythrocyte GSH content and serum vitamin E together with a positive correlation between erythrocyte GSH and serum vitamin E. A number of in vitro studies have demonstrated that both vitamins acted synergistically [19, 27], but in vivo, they could act independently as well [20]. As GSH is a water-soluble antioxidant, it probably has a higher affinity towards the reduction of the other water-soluble antioxidant (vitamin C) that to the lipid-soluble vitamin E. In our studies, serum MDA concentrations correlated positively with SOD activity. These two indices decreased in the group submitted to chemotherapy and antioxidants supplementation. According to RAY et al. [33] there is a relationship between SOD activity and blood reactive oxygen metabolites. The reduction of oxidative stress resulting from the administration of antioxidant vitamins was probably responsible for the less significant alterations in SOD levels in the second group. The observed positive relationship between vitamin E concentrations and GSH in group 2 could be attributed to the deficiency of glutathione that is used for reduction of the tocopheroxyl radical to tocopherol. The supplementation with vitamin E could deplete GSH, needed for this process [6, 19].

As a conclusion, the administration of antioxidants during the chemotherapy resulted in significant reduction of blood lipid peroxidation products (MDA) concentrations throughout the increase of tissue reduced glutathione consumption coupled to the sparing of some tissue antioxidants (tocopherols and at a lesser extend vitamin C) and increased activity of the SOD enzyme in erythrocytes. Consequently, the adjuvant antioxidant treatment would be beneficial in dogs with mammary adenocarcinomas by limiting the oxidative stress induced by anticancer drugs or directly by the carcinogenesis and by preserving the endogenous antioxidant defence systems, but further studies are required for comparing the clinical outcome (survival over 5 years, risk of relapse or secondary infection) in cancer dogs during chemotherapy supplemented or not with antioxidants.

References


