Fatal Liver and Bone Marrow Toxicity by Combination Treatment of Dichloroacetate and Artesunate in a Glioblastoma Multiforme Patient: Case Report and Review of the Literature

Martin Uhl¹, Stefan Schwab¹ and Thomas Efferth²*

¹Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany, ²Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany

A 52-year-old male patient was treated with standard radiochemotherapy with temozolomide for glioblastoma multiforme (GBM). After worsening of his clinical condition, further tumor-specific treatment was unlikely to be successful, and the patient sought help from an alternative practitioner, who administered a combination of dichloroacetate (DCA) and artesunate (ART). A few days later, the patient showed clinical and laboratory signs of liver damage and bone marrow toxicity (leukopenia, thrombocytopenia). Despite successful restoration of laboratory parameters upon symptomatic treatment, the patient died 10 days after the infusion. DCA bears a well-documented hepatotoxic risk, while ART can be considered as safe concerning hepatotoxicity. Bone marrow toxicity can appear upon ART application as reduced reticulocyte counts and disturbed erythropoiesis. It can be assumed that the simultaneous use of both drugs caused liver injury and bone marrow toxicity. The compassionate use of DCA/ART combination therapy outside of clinical trials cannot be recommended for GBM treatment.

Keywords: adverse side effects, cancer, chemotherapy, toxicology

INTRODUCTION

Glioblastoma multiforme (GBM) is an aggressive brain tumor that is currently treated with a combination of radiotherapy and temozolomide (TMZ) chemotherapy. The prognosis is unfavorable with an average survival of 15 months (1–3). In this desperate situation, it is not uncommon for patients to seek help outside standard medicine from alternative practitioners and healers. Often, non-approved remedies or unproven combination of drugs are prescribed, which occasionally may lead to undesired side effects or even life-threatening toxicities.

Dichloroacetate (DCA) is generated as by-product of chlorination of drinking water and by metabolization of drugs and chemicals (4). DCA accumulation in groundwater is considered as

Abbreviations: ARS, artemisinin; ART, artesunate; DCA, dichloroacetate; GBM, glioblastoma multiforme; TMZ, temozolomide; VA, valproic acid.
potential health hazard. In vitro and in vivo investigations showed that DCA inhibits tumor growth by redirecting glycolysis to oxidative phosphorylation and oxidative removal of lactate via pyruvate (5). Although five GBM patients have been previously treated with DCA (6), there is only limited knowledge about the efficacy or toxicity of DCA in cancer therapy.

In addition to their antimalarial activity, the artemisinin (ARS) derivatives [artesunate (ART), artemether, dehydroartemisinin] also exert anticancer activity in vitro and in vivo (7–13), including some brain tumor models (14–18). Compassionate use of ARS-type drugs encouraged the initiation of phase I/II trials in cancer patients (19–27). Most of these studies report are case reports or consist of only small numbers of patients. Therefore, there is still limited evidence regarding the safe use of ARS in cancer patients.

In the present case report, we describe a patient, who died with severe liver and bone marrow toxicity after intake of combined DCA and ART.

**CASE REPORT**

A 52-year-old male patient was diagnosed with GBM after suffering for several weeks from cognitive decline, headaches, gait ataxia, and a series of epileptic seizures. The initiation of adjuvant therapy was delayed by complicated wound healing, but finally – 53 days after surgery – radiotherapy up to 60 Gy of the tumor region was initiated with simultaneous TMZ chemotherapy (75 mg/m²) according to local guidelines (28).

The general state of health was unfavorable (Karnofsky score: 50). The patient suffered from right-side hemiparesis and...
required considerable help and medical assistance. Therefore, adjuvant TMZ chemotherapy was ruled out, and rehabilitation actions were initiated. Rehabilitation had to be discontinued 128 days after surgery, because of another series of epileptic seizures. Antiepileptic treatment was escalated to 1800 mg valproic acid (VA), 3000 mg levetiracetam, 200 mg lacosamide, and 20 mg clobazam. Progressive intracranial tumor burden by CT and Fet-PET scan diagnosis was considered as non-suited for tumor-specific treatment, and steroid medication was escalated. At that point, the patient and his family were seeking help from an alternative practitioner. An unknown amount of DCA was administered and ART (2.5 mg/kg bodyweight) was intravenously infused 148 days after surgery. At that time, the patient had a stable/unchanged concomitant medication. The patient's cognitive condition declined during the following days with adynamia, severe headaches, and psychomotoric retardation in rapid change with signs of delusions. After admission to the hospital, epileptic activity was not found by EEG and CT scanning did not show relevant changes concerning mass effect or edema. However, blood examinations showed signs of exsiccosis, pancytopenia, and markedly increased hepatic enzyme activities (Figure 1). Upon fluid substitution, laboratory parameter stabilized. However, two days after hospitalization, the state of the patient suddenly deteriorated with hypotension, systemic signs of infection, and a series of epileptic seizures. Discussing the need for intensified medical intervention and possible mechanical ventilation, the family did not wish these the actions to be undertaken according to the patient's provision. The patient died during the course of the following night and 157 days after surgery.

The timing of events can be summarized as follows:

- Surgery at day 0
- Start of radiotherapy 53 days after surgery
- End of radiotherapy 92 days after surgery
- Infusion of ART and DCA 148 days after surgery
- First signs of toxicity 154 days after surgery (elevated liver enzymes and hematotoxicity)
- Death of the patient 157 days after surgery

A valuable measure for the causality of adverse reactions of drugs in patients with liver injury is the Roussel Uclaf Causality Assessment Method (RUCAM) (29, 30). RUCAM considers all relevant criteria for liver injury by drugs. We applied the RUCAM scoring system to the patient presented here and found an overall quantitative grading of causality of 6, which indicates reasonable probability that the combinational administration of DCA and ART caused liver injury (Table 1).

## DISCUSSION

The severity and outcome of this case of compassionate use of alternative medication is remarkable. While the hepatotoxic potential of DCA is well documented, ART is actually consi-dered a rather safe antimalarial drug. It can be speculated that the specific combination of both drugs provoked fatal liver and bone marrow toxicity in the patient.

At the day of hospitalization, prior alternative medication had not been declared by the patient. Therefore, liver toxicity by VA or TMZ has been suspected. In the past, severe and even fatal toxic-ity were reported for both for VA (31–36) and for TMZ (37–40). Taking into account the additional sudden decline in leukocyte and thrombocyte counts during the next days and considering the prior normal values made this possibility, however, rather unlikely. The dynamics of TMZ- or VA-caused liver damage usually represent more continuous processes. The nadir of TMZ is expected after 21 days. Even delayed forms of bone marrow toxic-ity are not comparable to the dramatic decline observed here.

The cause of death remains speculative, since an autopsy was not performed in accordance to the patient's provision and family wishes. We consider aspiration pneumonia or spontaneous internal bleeding as possible causes for the sudden decline of blood pressure.

As shown in Table 2, DCA administration in animal experiments induced hepatotoxicity and hepatocarcinogenesis. DCA increased hepatic oxidative stress and disturbed liver metabolism. Although treatment of five GBM patients with DCA did not reveal hepatotoxicity (6), there is evidence from preclinical in vivo experiments that DCA affects the liver (Table 2) (4, 41). However, a straightforward conclusion to the observed hepatotoxicity in the present case is difficult, because the dose of applied DCA to the patient was not disclosed by the alternative practitioner.

The clinical safety of ART is well documented. Large clinical trials and meta-analyses of clinical trials dealing with many thousands of malaria patients did not unravel serious adverse effects (59, 60). Preclinical toxicity studies gave some hints for neurotoxinicity, embryotoxicity, genotoxicity, hematotoxicity, cardiotoxicity, nephrotoxicity, and allergic reaction (61). Long-term application of low ARS concentrations may be more toxic than short-term application of high doses. This may explain, why toxicities can

| Criterion | Observation | Given score | Score range |
|-----------|-------------|-------------|-------------|
| 1. Time to onset of the reaction | Toxic reaction 6 days after treatment | 2 | (1 to +3) |
| 2. Course of the reaction | Decrease ≤50% within 30 days | 3 | (−2 to +3) |
| 3. Risk factors for drug reaction | Age of patient ≥55 years | 0 | (0 to +1) |
| 4. Concomitant drugs | No information | 0 | (−3 to 0) |
| 5. Non-drug-related causes | HAV, HBV, and HCV serology missing, no biliary obstruction, no alcoholism, no hypotension | 0 | (−3 to +2) |
| 6. Previous information on the drug | Hepatotoxicity published, but unlabeled | 1 | (0 to +2) |
| 7. Response to readministration | Not possible, because patient died | 0 | (−2 to +3) |

Quantitative grading of causality: ≤1, excluded; 1–2, unlikely; 3–5, possible; 6–8 probable; ≥9, highly probable.

---

**Table 1**: Causality assessment for adverse reactions to the DCA/ART combination treatment according to RUCAM (29, 30).
TABLE 2 | Literature survey on hepatotoxicity by DCA in vivo.

| Experimental model | Treatment dose | Route of administration | Duration of treatment | Effect | Reference |
|--------------------|----------------|-------------------------|-----------------------|--------|-----------|
| Dogs               | 300 mg/kg      | Intravenously           | 1 h                   | Decrease of tissue lactate levels in liver | (42)     |
| B6C3F1 mice        | 1–2 g/L        | Drinking water          | 52 weeks              | Enlarged livers, cytomegaly, and glycogen accumulation | (43)     |
| B6C3F1 and Swiss-Webster mice | 300–2000 mg/L | Drinking water          | 14 days               | Tumorigenesis is influenced by necrosis and reparative hyperplasia, increased ^3H-thymidine labeling index | (44)     |
| B6C3F1 mice        | 200–600 mg/L   | Drinking water          | 72 h                  | Markedly enlarged liver, cytomegaly, glycogen accumulation, recurrent liver necrosis with high proliferation rates, peroxisome induction, and lipofuscin accumulation | (45)     |
| B6C3F1 mice        | 2.0 g/L        | Drinking water          | 38 or 50 weeks        | Induction of hepatocellular lesions with increased cell divisions; increased c-Jun/c-Fos expression | (46)     |
| B6C3F1 mice        | 0.5 g/L        | Drinking water          | 2 weeks               | 4-fold increase of in vitro colony formation of hepatocytes suggesting promotion of clonal expansion of anchorage-independent hepatocytes in vivo | (47)     |
| B6C3F1 mice        | 2 g/L          | Drinking water          | 48 weeks              | Increase of tumor growth rates | (48)     |
| B6C3F1 mice        | 0.2–3 g/L      | Drinking water          | 4–12 weeks            | Increase of glycogen concentration in liver | (49)     |
| B6C3F1 mice        | 0.1–2 g/L      | Drinking water          | 2–10 weeks            | Reduction of serum insulin, downregulation of insulin receptor, and increased MAP kinase phosphorylation | (50)     |
| B6C3F1 mice        | 0.5 or 2 g/L   | Drinking water          | 35–52 weeks           | Induction of liver tumors, which were c-Jun-positive | (51)     |
| Fischer-344 rats   | 0.05–20 mg/kg  | Intravenously or by gavage | 7 days                | Oral bioavailability was 0–13% in control rats and 14–75% in GSTZ-depleted rats | (52)     |
| Sprague-Dawley rats| 2.5 μg–50 mg/kg/day | Drinking water | 12 weeks             | GSTZ1-1 activity and expression decreased to 95–100% and recovered 8 weeks after cessation | (53)     |
| B6C3F1 mice        | 300 mg/kg      | By gavage               | 6 or 12 h             | Increased production of superoxide anion, lipid peroxidation, and DNA-single strand breaks | (54)     |
| B6C3F1 male mice   | 7.7–410 mg/kg/day | By gavage            | 4 or 13 weeks         | Hepatomegaly at 410 mg/kg/day. Dose-dependent increase of SOD activity, lipid peroxidation, and DNA-single strand breaks | (55)     |
| Sprague-Dawley rats| 500 mg/kg/day  | By gavage               | 8 weeks               | Dechlorination of DCA was higher in cytosol than in mitochondria by GSTZ1 | (56)     |
| PKD rats           | 75 mg/L        | Drinking water          | 8 weeks               | Only male rats with polycystic kidney disease (PKD) showed increased disease severity (cystic enlargement and proteinuria) | (57)     |
| B6C3F1 mice        | 7.5–30 mg/kg/day | By gavage            | 13 weeks              | Dose-dependent increase of SOD production, lipid peroxidation and DNA-single strand breaks | (58)     |

be observed in animal experiments, but not in human studies. A large meta-analysis with 5000 malaria patients revealed that hepatotoxicity was a rare event, and elevated liver enzymes have been found in 0.9% of all cases (39). Although most papers on clinical safety were published in the context of malaria treatment, there are also some reports on the use of ARS-derivatives in cancer patients. Case reports on the compassionate use of ART or artemether in patients, with laryngeal squamous cell carcinoma, uveal melanoma, pituitary macroadenoma, and prostate carcinoma, reported that the ARSs were well tolerated with no additional side effects in addition to those caused by standard chemotherapy. A randomized controlled trial with 120 advanced non-small cell lung cancer patients on vinorelbine alone versus vinorelbine plus ART did not find significant differences in toxicity between the two treatment groups (23). In a pilot phase I/II trial in 10 patients suffering from cervical carcinoma, arteminol reduced clinical symptoms, vaginal discharge, and pain, and no adverse events of grade 3 and 4 were observed (24). Another phase I/II pilot study in veterinary cancers was conducted in 23 dogs with non-resectable tumors. No neurological or cardiac toxicity was observed, and seven dogs exhibited no adverse effects at all. Fever and hematological or gastrointestinal toxicity, mostly transient, occurred in 16 dogs. One dog died from treatment-unrelated pneumonia (25). As reported from a randomized, double-blind placebo-controlled pilot study in 23 colorectal cancer patients, oral ART therapy was well tolerated without signs of hepatotoxicity (26). Another recent phase I trial on 23 metastasized breast cancer patients reported that four patients had adverse events of the auditory system possibly related to the intake of ART. However, none of these side effects were severe adverse events. Four patients had adverse events concerning the vestibular system, one of which was severe, but fully reversible after discontinuation of ART treatment (27). In summary, hepatotoxicity has not been found in any of these patients.

Hematotoxicity is worth mentioning in this context, because the patient suffered from reduced leukocyte and thrombocyte counts. The toxicity of ARS-type drugs on leukopoiesis is controversially discussed, and both enhanced and inhibited leukocyte functions have been observed (61). Dihydroartemisinin ameliorated inflammatory disease (62). However, ARS-derivatives exhibited higher cytotoxicity in vitro toward hematopoietic progenitor cells of the granulocyte-monocyte lineage (CFU-GM)
than toward cancer cells (63), indicating that myelosuppression might be an issue in cancer therapy. While thrombocytopenia was apparently not relevant, damage of erythrocytes occurred in animal experiments (61). A sensitive measure for erythropoiesis is the blood count of reticulocytes in peripheral blood. Reduced reticulocyte counts (as erythrocyte precursors) have not only been observed in vitro and in animals, but also in human patients upon treatment with ARS-type drugs (59, 61, 64, 65).

REFERENCES

1. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol (2009) 10(5):459–66. doi:10.1016/S1470-2243(09)70025-7
2. Woehler A, Bauchet L, Barnholtz-Sloan JS. Glioblastoma survival: has it improved? Evidence from population-based studies. Curr Opin Neurol (2014) 27(6):666–74. doi:10.1097/WCO.0000000000000144
3. Yang LJ, Zhou CF, Lin ZX. Temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme: a systematic review. Cancer Invest (2014) 32(2):31–6. doi:10.3109/07357907.2013.861474
4. Stacpoole PW, Henderson GN, Yan Z, James MO. Clinical pharmacology and toxicology of dichloroacetate. Environ Health Perspect (1998) 106(Suppl 4):989–94. doi:10.1289/ehp.981069489
5. Kankotia S, Stacpoole PW. Dichloroacetate and cancer: new hope for an orphan drug? Biochim Biophys Acta (2014) 1846(2):617–29. doi:10.1016/j.bjba.2014.08.005
6. Michelakis ED, Sutendra G, Dromparis P, Webster L, Haromy A, Niven E, et al. Metabolic modification of glioblastoma with dichloroacetate. Sci Transl Med (2010) 2(31):31ra34. doi:10.1126/scitranslmed.3000677
7. Moore JC, Lai H, Li JR, Ren RL, McDougall JA, Singh NP, et al. Oral administration of dihydroartemisinin and ferrous sulfate retarded implanted fibrosarcoma growth in the rat. Cancer Lett (1995) 98(1):83–7. doi:10.1016/0304-3835(95)03999-D
8. Effert T, Rücker G, Falkenberg M, Manns D, Olbrich A, Fabry U, et al. Detection of apoptosis in KG-1a leukemic cells treated with investigational drugs. Arzneimittelforschung (1996) 46(2):196–200.
9. Effert T, Dunstan H, Sauerbrey A, Miyoshi H, Chittambar CR. The anti-malarial artemisin is also active against cancer. Int J Oncol (2001) 18(4):767–73.
10. Effert T, Olbrich A, Bauer R. mRNA expression profiles for the response upon treatment with ARS-type drugs (59, 61, 64, 65).
In conclusion, the presented case illustrates the possible consequences of compassionate use of non-approved drugs or unproven drug combinations. Drug therapy should always be in accordance to the guidelines of good clinical practice.

AUTHOR CONTRIBUTIONS

MU and SS: treated the patient. TE: wrote the paper.

16. Wu ZP, Gao CW, Wu YG, Zhu QS, Yan C, Xin L, et al. Inhibitive effect of artemether on tumor growth and angiogenesis in the rat C6 orthotopic brain gliomas model. Int J Cancer (2009) 8(1):88–92. doi:10.1002/ijc.2373540.8330714
17. Berdelle N, Nikolova T, Quiros S, Efferth T, Kaina B. Artesunate induces oxidative DNA damage, sustained DNA double-strand breaks, and the ATM/ATR damage response in cancer cells. Mol Cancer Ther (2011) 10(12):2224–33. doi:10.1158/1535-7163.MCT-11-0583
18. Chen J, Chen X, Wang F, Gao H, Hu W. Dihydroartemisinin suppresses glioma proliferation and invasion via inhibition of the ADAM17 pathway. Neurosurg Sci (2015) 36(3):435–40. doi:10.1007/s10072-014-1963-6
19. Singh NP, Verma KB. Case report of a laryngeal squamous cell carcinoma treated with artesunate. Arch Oncol (2002) 2(1):729–80. doi:10.2298/ AOO0204279S
20. Berger TG, Dieckmann D, Efferth T, Schultz ES, Funk JO, Baur A, et al. Artesunate in the treatment of metastatic uveal melanoma – first experiences. Oncol Rep (2005) 14(6):599–603.
21. Singh NP, Panwar VK. Case report of a pituitary macroadenoma treated with artemether. Int J Tumor Biol (2006) 5:391–4. doi:10.1158/1940-0314.IJTPB-293511
22. Michaelsen FW, Saeed ME, Schwarzkopf J, Efferth T. Activity of Artemisia annua and artemisinin derivatives, in prostate carcinoma. Phytomedicine (2015) 22(14):1223–31. doi:10.1016/j.phymed.2015.11.001
23. Zhang ZY, Yu SQ, Mao LY, Huang XY, Zhang XP, Zhu YP, et al. Artesunate combined with vinorelbine plus cisplatin in treatment of advanced Non-small cell lung cancer: a randomized controlled trial, Zhong Xi Yi Jie He Xue Bao (2008) 6(2):134–8. doi:10.3736/jcim20080206
24. Jansen FH, Adoubi I, Kouassi JC, DE C, Jansen N, Tschulakow A, et al. First study of oral Artinem®-R in advanced cervical cancer: clinical benefit, tolerability and tumor markers. Anticancer Res (2011) 31(12):4417–22.
25. Rutteman GR, Erlich SA, Mol JA, Spee B, Grimvis GC, Fleckenstein L, et al. Safety and efficacy field study of artesunate for dogs with non-rectalce tumours. Anticancer Res (2013) 33(5):1819–27.
26. Krishna S, Ganapathi S, Ster IC, Saeed ME, Cowan M, Finlayson C, et al. A randomised, double blind, placebo-controlled pilot study of oral artemesate therapy for colorectal cancer. EBioMedical (2015) 2(1):82–90. doi:10.3736/jcim2014.11.010
27. König M, von Hagens C, Hoth S, Baumann I, Walter-Sack I, Edler L, et al. Investigation of ototoxicity of artemisin in as add-on therapy in patients with metastatic or locally advanced breast cancer: new audiological results from a prospective, open, uncontrolled, monocentric phase I study. Cancer Chemother Pharmacol (2016) 77(2):413–27. doi:10.1007/s00280-016-2960-7
28. Weller M, van den Bent M, Hopkins K, Tonon JC, Stupp R, Falini A, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol (2014) 15(9):e395–403. doi:10.1016/S1470-2243(14)70011-7
29. Danan G, Benichou C. Causality assessment of adverse reactions to drugs – 1. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol (1993) 46(11):1233–30. doi:10.1016/0895-4356(93)90101-6
30. Tischke RLD, Melchart D, Danan G. Traditional Chinese Medicine (TCM) and herbal hepatotoxicity: RUCAM and the role of novel diagnostic biomarkers such as MicroRNAs. Medicines (2016) 3(3):18. doi:10.3390/medicines 3030018
31. Hjelm M, de Silva LV, Seakins JW, Oberholzer VG, Rolles CJ. Evidence of inherited urea cycle defect in a case of fatal valproate toxicity. Br Med J (Clin Res Ed) (1986) 292(6512):23–4. doi:10.1136/bmj.292.6512.23
47. Stauber AJ, Bull RJ, Thrall BD. Dichloroacetate and trichloroacetate promote
49. Kato-Weinstein J, Stauber AJ, Orner GA, Thrall BD, Bull RJ. Differential
50. Lingohr MK, Thrall BD, Bull RJ. Effects of dichloroacetate (DCA) on serum
32. Evans RJ, Miranda RN, Jordan J, Krolikowski FJ. Fatal acute pancreatitis
35. Pronicka E, Weglewskia-Jurkiewicz A, Pronicki M, Sykut-Cegielska J, Kowalski
38. George BJ, Eichinger JB, Richard TJ. A rare case of aplastic anemia
34. Acharya S, Bussel JB. Hematologic toxicity of sodium valproate.
68. Clark RL. Effects of artemisinins on reticulocyte count and relationship to pos-
56. Li W, James MO, McKenzie SC, Calcutt NA, Liu C, Stacpoole PW. Mitochondrion
53. Guo X, Dixit V, Liu H, Shroads AL, Henderson GN, James MO, et al. A
52. Saghir SA, Schultz IR. Low-dose pharmacokinetics and oral bioavailability of
dichloroacetate in naive and GST-zeta-depleted rats. Environ Health Perspect
54. Hassoun EA, Dey S. Dichloroacetate- and trichloroacetate-induced phagocytic
61. Efferth T, Kaina B. Toxicity of the antimalarial artemisinin and its derivatives.
64. Wootton DG, Opara H, Biagini GA, Kanjala MK, Duparc S, Kirby PL, et al.
60. Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N. Artesunate
57. Gattone VH II, Bacallao RL. Dichloroacetate treatment accelerates the
development of pathology in rodent autosomal recessive polycystic kidney
disease. Am J Physiol Renal Physiol (2014) 307(2):F114–5. doi:10.1152/
40. Grieco A, Tafuri MA, Biolato M, Diletto B, Di Napoli N, Balducci N, et al.
65. Clark RL. Effects of artemisinins on reticulocyte count and relationship to pos-
55. Hassoun EA, Cearfoss J, Spildener J. Dichloroacetate- and trichloroacetate-
63. Beekman AC, Wierenga PK, Woerdenbag HJ, Van Uden W, Pras N,
62. Clark RL. Effects of artemisinins on reticulocyte count and relationship to pos-
43. Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N. Artesunate
58. Li W, James MO, McKenzie SC, Calcutt NA, Liu C, Stacpoole PW. Mitochondrion
36. Star K, Edwards IR, Choonaar L. Dichloroacetate and valproic acid in children:
a review of individual case safety reports in VigiBase. PLoS One (2014)
42. Graf H, Leach W, Arieff AI. Effects of dichloroacetate in the treatment of
30. Miller JH, Minard K, Wind RA, Orner GA, Sasser LB, Bull RJ. In vivo MRI
48. Graf H, Leach W, Arief AI. Effects of dichloroacetate in the treatment of
31. Beekman AC, Wierenga PK, Woerdenbag HJ, Van Uden W, Pras N,
45. Kato-Weinstein J, Stauber AJ, Orner GA, Thrall BD, Bull RJ. Differential
49. Lingohr MK, Thrall BD, Bull RJ. Effects of dichloroacetate (DCA) on serum
58. Li W, James MO, McKenzie SC, Calcutt NA, Liu C, Stacpoole PW. Mitochondrion
33. Beekman AC, Wierenga PK, Woerdenbag HJ, Van Uden W, Pras N,
50. Lingohr MK, Thrall BD, Bull RJ. Effects of dichloroacetate (DCA) on serum
51. Bull RJ, Orner GA, Cheng RS, Stillwell L, Stauber AJ, Sasser LB, et al.
44. Graf H, Leach W, Arief AI. Effects of dichloroacetate in the treatment of
41. Bell RJ. Mode of action of liver tumor induction by trichloroethyle and its
metabolites, trichloroacetate and dichloroacetate. Environ Health Perspect
(2000) 108(Suppl 2):241–59. doi:10.1289/ehp.10082241
46. Graf H, Leach W, Arief AI. Effects of dichloroacetate in the treatment of
hypoxic lactic acidosis in dogs. J Clin Invest (1985) 76(5):919–23. doi:10.1172/
43. Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N. Artesunate
66. Wootton DG, Opara H, Biagini GA, Kanjala MK, Duparc S, Kirby PL, et al.
67. Wootton DG, Opara H, Biagini GA, Kanjala MK, Duparc S, Kirby PL, et al.
68. Clark RL. Effects of artemisinins on reticulocyte count and relationship to pos-
53. Guo X, Dixit V, Liu H, Shroads AL, Henderson GN, James MO, et al. Inhibition
and recovery of rat hepatic glutathione S-transferase zeta and alteration of tyrosine metabolism following dichloroacetate exposure and withdrawal. Drug Metab Dispos (2006) 34(1):36–42. doi:10.1124/dmd.003.
30. Miller JH, Minard K, Wind RA, Orner GA, Sasser LB, Bull RJ. In vivo MRI
measurements of tumor growth induced by dichloroacetate: implications for mode of action. Toxicology (2000) 145(2–3):115–25. doi:10.1016/S0300-483X(00)00148-7
45. Kato-Weinstein J, Stauber AJ, Orner GA, Thrall BD, Bull RJ. Differential
effects of dihalogenated and trihalogenated acetates in the liver of B6C3F1 mice. J Appl Toxicol (2001) 21(2):81–9. doi:10.1002/jat.717
40. Grieco A, Tafuri MA, Biolato M, Diletto B, Di Napoli N, Balducci N, et al.
30. Miller JH, Minard K, Wind RA, Orner GA, Sasser LB, Bull RJ. In vivo MRI
measurements of tumor growth induced by dichloroacetate: implications for mode of action. Toxicology (2000) 145(2–3):115–25. doi:10.1016/S0300-483X(00)00148-7
45. Kato-Weinstein J, Stauber AJ, Orner GA, Thrall BD, Bull RJ. Differential
effects of dihalogenated and trihalogenated acetates in the liver of B6C3F1 mice. J Appl Toxicol (2001) 21(2):81–9. doi:10.1002/jat.717
40. Grieco A, Tafuri MA, Biolato M, Diletto B, Di Napoli N, Balducci N, et al.
30. Miller JH, Minard K, Wind RA, Orner GA, Sasser LB, Bull RJ. In vivo MRI
measurements of tumor growth induced by dichloroacetate: implications for mode of action. Toxicology (2000) 145(2–3):115–25. doi:10.1016/S0300-483X(00)00148-7
45. Kato-Weinstein J, Stauber AJ, Orner GA, Thrall BD, Bull RJ. Differential
effects of dihalogenated and trihalogenated acetates in the liver of B6C3F1 mice. J Appl Toxicol (2001) 21(2):81–9. doi:10.1002/jat.717
40. Grieco A, Tafuri MA, Biolato M, Diletto B, Di Napoli N, Balducci N, et al.
30. Miller JH, Minard K, Wind RA, Orner GA, Sasser LB, Bull RJ. In vivo MRI
measurements of tumor growth induced by dichloroacetate: implications for mode of action. Toxicology (2000) 145(2–3):115–25. doi:10.1016/S0300-483X(00)00148-7
45. Kato-Weinstein J, Stauber AJ, Orner GA, Thrall BD, Bull RJ. Differential
effects of dihalogenated and trihalogenated acetates in the liver of B6C3F1 mice. J Appl Toxicol (2001) 21(2):81–9. doi:10.1002/jat.717