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Cyanide and lactate levels in patients during chronic oral amygdalin intake followed by intravenous amygdalin administration

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ABSTRACT

The natural compound amygdalin has gained high popularity among tumor patients as a complementary or alternative treatment option. However, due to metabolization of amygdalin to cyanide (HCN) following oral consumption, there could be a high risk of lactic acidosis caused by cyanide intoxication. The present retrospective study was undertaken to evaluate cyanide blood and lactate plasma levels of tumor patients (n = 55) before and after intravenous (i.v.) amygdalin infusion. All patients had also continuously ingested amygdalin tablets (3 x 500 mg/day), excepting on the days of i.v. administration. Each patient received one to five intravenous amygdalin treatments. The time period between each i.v. application ranged between 4–6 days. The initial i.v. dose was 6 mg (n = 28), 9 mg (n = 1), 15 mg (n = 1) or 18 mg (n = 25). The mean cyanide blood level before i.v. amygdalin administration was 34.74 µg/L, which increased significantly to a mean value of 66.20 µg/L after i. v. amygdalin application. In contrast, lactate decreased significantly from 1266 µmol/L pre-infusion to 868 µmol/L post-infusion. Increasing i.v. amygdalin by 1 mg was also associated with a significant increase in the cyanide level, while the lactate blood level significantly decreased. This is the first study evaluating cyanide levels under conditions employed by amygdalin administrators, i.e. after chronic oral amygdalin intake and then again after a closely subsequent intravenous amygdalin administration. Since lactate decreased, whilst cyanide increased, it is concluded that elevation of cyanide does not induce metabolic acidosis in terms of an increased lactate level.

1. Introduction

Complementary and alternative medicine (CAM) has gained high popularity among tumor patients, whereby the use of plant derived substances is a commonly applied CAM-method with a prevalence of about 50%.[1–3] According to the definition of the National Center of Complementary and Integrative Health (NCCIH), “complementary” is related to a non-mainstream practice used together with conventional medicine, whereas “alternative” has been defined as a non-mainstream practice used in place of conventional medicine.[4] Clinical studies related to the therapeutic efficacy of specific plant products are sparse and well-designed, evidence based clinical trials are lacking. The discrepancy between the use of a natural compound and knowledge about its anti-tumor properties is notable for the cyanogenic diglucoside, amygdalin (D-mandelonitrile-β-D-glucosido-6-β-D-glucoside), derived from the fruit kernels of Rosaceae species such as peach, apricot, and bitter almond. At least 35 clinics or medical practices in Germany offer an amygdalin based tumor therapy, as shown by an incomplete list compiled by the German Federal Institute for Drugs and Medical Devices (BfArM).[5]

Amygdalin is administered orally and/or intravenously (i.v.). Orally consumed amygdalin is metabolized to D-mandelonitrile β-D-glucoside (prunasin) in the gastrointestinal tract by β-glucosidase driven cleavage of the terminal glucose residue. Prunasin can further be degraded by β-glucosidase into mandelonitrile, which dissociates into cyanide and benzaldehyde.[6] Cyanide is then rapidly converted into thiocyanate, catalyzed by rhodanese (syn.: thiosulfate sulfurtransferase).[7] Cyanide is highly toxic, binding to Fe^{3+} of mitochondrial cytochrome oxidase a3, thereby blocking the electron transport chain and oxidative metabolism. Inhibition of oxidative phosphorylation finally causes a shift from

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aerobic to anaerobic metabolism with cellular ATP depletion and lactic acidosis. Since intravenously administered amygdalin bypasses enzymatic degradation in the gastrointestinal tract, amygdalin associated cyanide toxicity is thought to be avoided by i.v. administration.

Proponents of amygdalin therapy claim that amygdalin leads to selective tumor cell cyanide poisoning due to tumor-specific abberations: enrichment of β-glucosidase coupled to a loss of the detoxifying enzyme rhodanese. Opponents of amygdalin therapy, however, warn that amygdalin may cause severe toxicity through systemic cyanide accumulation. Isolated reports on cyanide poisoning connected to amygdalin administration have been reported.[8] On the other hand, a clinical trial has not revealed any signs of cyanide toxicity.[9–11]

The present retrospective study was designed to evaluate cyanide levels of patients who were administered oral amygdalin, closely followed by intravenous amygdalin administration. Since a European expert consensus and others have recommended evaluating lactate alterations as an indication of cyanide poisoning,[12,13] lactate levels were also evaluated.

2. Material and methods

2.1. Patients

55 patients 25 (45%) men, 30 (55%) women, youngest 29 years old, oldest 83 (mean age: 57.7 years) were included in this retrospective study in a private practice in Germany, from 2015 to 2017. The study was approved by the ethics committee of the Hessian regional medical board, Frankfurt/Main, Germany **(FF 148/2017)**. 13 (23.6%) patients were being treated for urologic cancer (prostate, kidney, urinary bladder tumor), 17 (30.9%) for gynecologic cancer (breast, ovarian), 14 (25.5%) for gastro-intestinal tumors (rectum, colon, anal, liver, pancreas), 2 (3.6%) for dermatologic cancer and 9 (16.4%) patients had other types of cancer (lymphoma, tongue cancer) (Table 1).

2.2. Oral amygdalin administration

All patients continuously ingested amygdalin tablets (3 x 500 mg/day, Flora Pharmacy, Hannover, Germany), excepting on the days when i.v. amygdalin was administered. The time point of the first oral amygdalin administration was not documented. **There was also no exact information on whether amygdalin was applied alternatively or complementarily to each patient**.

2.3. Intravenous amygdalin administration

Each patient received one to five intravenous amygdalin treatments. The time period between each application ranged between 4–6 days. Overall, 97 administrations of amygdalin were recorded. Intravenous amygdalin was administered to 26 patients (47.2%) only once, to 21 patients (28.2%) twice, to 5 (9%) patients three times, to 2 patients (3.6%) 4 times, and to 2 patients (1.8%) 5 times (Table 2).

28 patients (51%) received 6 mg amygdalin as the initial dose. One patient received 9 and one patient 15 mg amygdalin. 25 patients (46%) initially received 18 mg amygdalin. A second dose was administered to 29 patients, whereby the majority of 25 patients (86%) received 30 mg amygdalin. 20% (n = 3) received 18 mg and 3.4% (n = 1) 15 mg of amygdalin. A third application was limited to 8 patients. 75% (n = 6) of these patients received 18 mg amygdalin, one patient received 15 mg and one patient 30 mg. 18 mg amygdalin was administered at the fourth (n = 3) and fifth (n = 1) treatment cycles.

Table 1
Tumor type.

Type of Tumor	Number of Patients	%
Urologic	13	23.6
Gynecologic	17	30.9
Dermatologic	2	3.6
Gastrointestinal	14	25.5
Other	9	16.4

Table 2
Number of i. v. amygdalin applications per patient.

Number of i. v. applications	Number of Patients	%
1	26	47.3
2	21	38.2
3	5	9.1
4	2	3.6
5	1	1.8

2.4. Measurement of cyanide, thiocyanate and lactate

Blood was drawn **in the private practice** for the measurement of cyanide (µg/L; blood), thiocyanate (mg/L; serum) and lactate (µmol/L; plasma) before and after each intravenous treatment with amygdalin. **Analysis was carried out by the MVZ Medizinisches Labor Bremen GmbH, Bremen, Germany, according to a standard protocol. To guarantee specimen stability, the time interval between sampling and analysis was under 24 h**.

2.5. Statistics

Statistical analysis was performed using the statistics program BiAS 10.04. (BiAS for Windows, EPSiLON-Verlag, Frankfurt am Main, Germany) for Wilcoxon matched pairs test. p values < 0.05 are considered to indicate a significant difference.

The statistical analysis for repeated measures correlation and mixed effect model calculation was conducted using R software (version 3.1.4, The R Foundation for Statistical Computing, Vienna, Austria). p values < 0.05 indicated a significant trend.

3. Results

The mean cyanide blood level before i.v. amygdalin administration (n = 97) was 34.74 µg/L (range: 17–305 µg/L, SD: 35.86 µg/L), which increased significantly ($p = 0.000001$) to a mean value of 66.20 µg/L (range: 24–517 µg/L, SD: 80.40 µg/L) after i. v. amygdalin application (Fig. 1A).

Lactate decreased significantly ($p = 0.00001$) from 1266.1 µmol/L (range: 469–3259 µmol/L, SD 542.4 µmol/L) pre-infusion to 867.7 µmol/L (range 201–2139 µmol/L, SD 389.0 µmol/L) post-infusion (Fig. 1B).

No significant change ($p = 0.363528$) in the mean thiocyanate blood level was seen (11.9 mg/L (pre-infusion) vs. 11.3 mg/L (post-infusion) (Fig. 1C).

The multivariate statistical analysis identified the i.v. amygdalin dose to be a significant predictor of the blood level of cyanide ($p < 0.001$) and lactate ($p < 0.001$). Importantly, both parameters responded contrarily to escalating i.v. amygdalin dosage. Increasing the dose of amygdalin by 1 mg was associated with a significant increase in the cyanide level ($p = 0.007$), while the lactate blood level significantly ($p = 0.005$) decreased.

Number of i.v amygdalin applications was not a predictor for cyanide ($p = 0.183$) or lactate ($p = 0.26$) level. Gender, age, and tumor entity were also non-significant variables for both cyanide and lactate ($p > 0.05$).

The repeated measures correlation (Fig. 2) determining the overall within- individual relationship between the paired cyanide and lactate blood levels after i.v. amygdalin administration on two or more occasions demonstrated no significant correlation between the blood values of cyanide and lactate ($p = 0.68786$, $r = 0.063$). Thus, these two blood

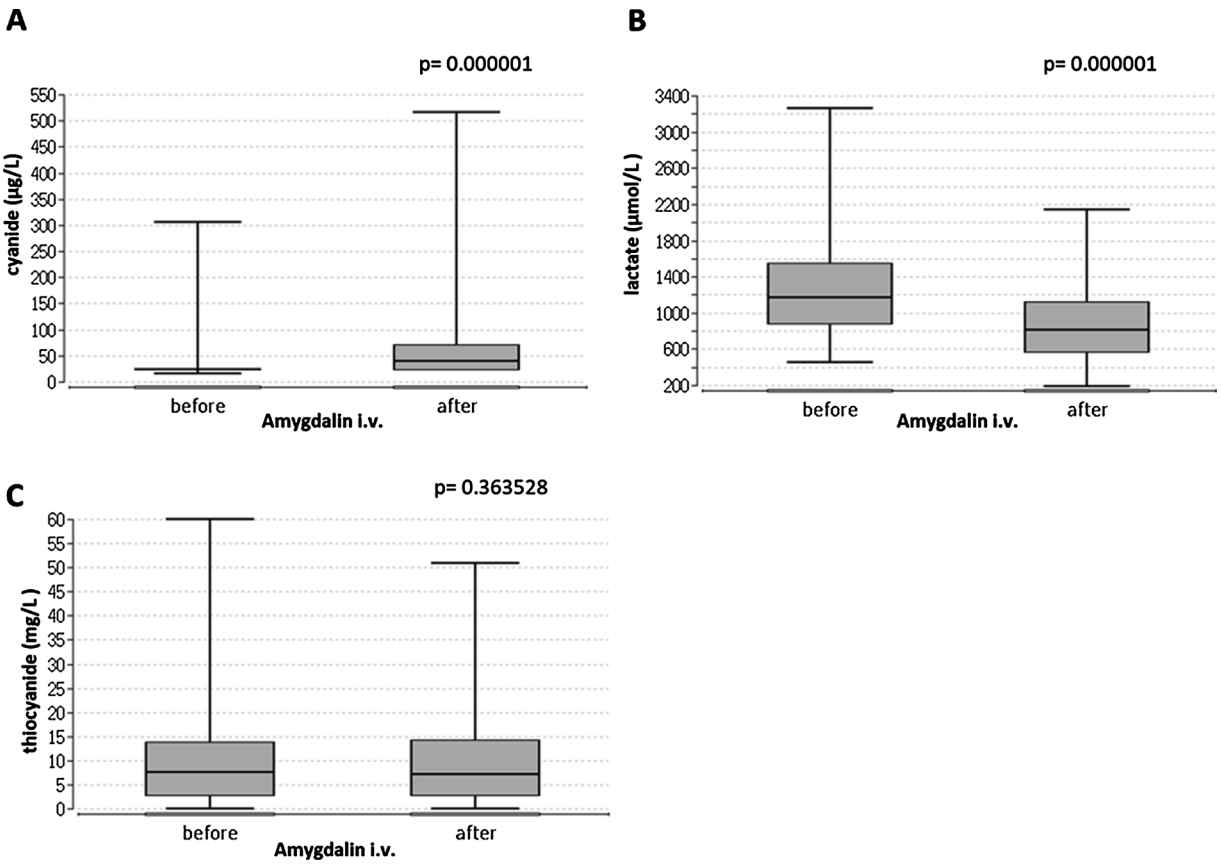

Fig. 1. (A) cyanide, (B) lactate and (C) thiocyanate levels before and after i. v. application of amygdalin (values are means).

values show no cumulative correlation after amygdalin administration when including and analyzing all application cycles.

Each patient was interviewed and examined before and after each application of i.v. amygdalin. No patient complained of nausea, feeling ill or experiencing any other clinical symptoms indicating severe cyanide intoxication such as dizziness or loss of consciousness. Measurement of blood pressure and heart rate revealed no pathological findings.

4. Discussion

The natural compound, amygdalin, administered orally and intravenously, is highly popular among tumor patients. However, several cases of cyanide toxicity after amygdalin administration have been documented, most being due to amygdalin overdosing. A recent report of acute cyanide poisoning was related in a 4-year-old child being administered "unquantified amounts" of amygdalin i.v. in addition to oral amygdalin (4 × 500 mg/day) plus apricot kernels (5–10/day).[14] Shortly after swallowing about 12 g amygdalin, another patient

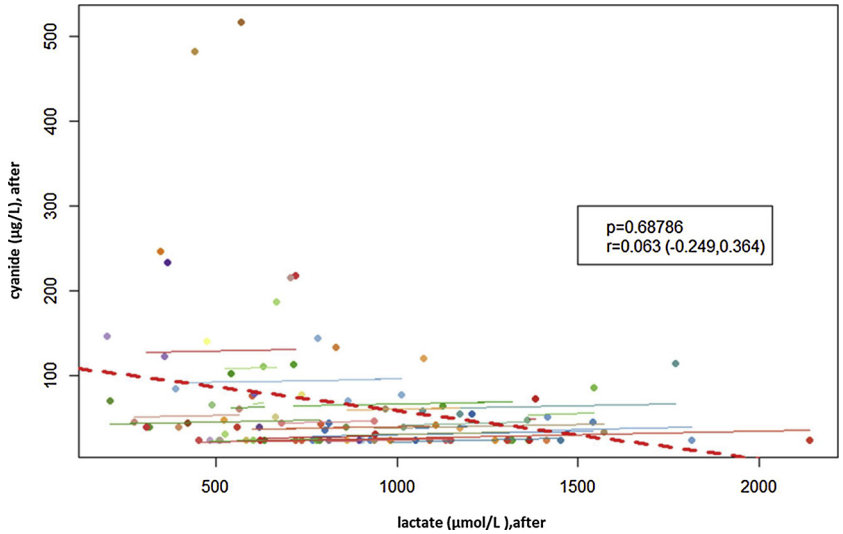

Fig. 2. Repeated measures correlation determining the overall within- individual relationship between paired cyanide and lactate blood levels after amygdalin i.v. administration on two or more occasions.

developed dizziness, became comatose and died a day later.[15] A detailed overview about toxic cases is given in.[8]

Orally administered amygdalin is subject to gut microbial β-glucosidase activity, which primarily drives amygdalin metabolization[8] and results in measurable blood cyanide levels.[9] On the other hand, it has been reported that i. v. amygdalin (4.5 g/m2/day) is largely excreted unchanged in the urine, producing no clinical or laboratory evidence of toxicity due to cyanide.[10] Ames et al. has also detected no increase in cyanide plasma concentrations in patients treated with i. v. amygdalin,[11] with the amygdalin being excreted unchanged in the urine.[16]

The cyanide levels in the present retrospective evaluation were measured under conditions employed by amygdalin administrators, i.e. after chronic oral amygdalin intake and then again after a closely subsequent intravenous amygdalin administration. Under these conditions, cyanide was measurable before amygdalin was administered intravenously. In contrast to the Ames study, i. v. administration of amygdalin in the present retrospective study significantly enhanced the blood cyanide level. The reason for this finding is not clear. Based on a rat model, i. v. application of amygdalin has been associated with an increased urine output of thiocyanate, indicating that at least moderate metabolization occurs independently of gut flora activity.[17] Since the further increase of cyanide observed immediately after i. v. administration cannot be attributed to the oral amygdalin in our study, a specific mechanism must be assumed. In fact, amygdalin's conversion to cyanide may depend on the route of administration, which opens the question of where conversion of amygdalin to cyanide/thiocyanate takes place when applied intravenously. If β-glucosidase is enriched in tumor cells, cyanide could hypothetically accumulate following cellular amygdalin uptake and then be released into the blood when the tumor cells are destroyed. Although β-glucosidase has been detected in several tumor cell lines,[18,19] β-glucosidase enrichment in tumor tissue has not yet been demonstrated.

Evidence is presented here that cyanide becomes elevated after patients receive amygdalin i.v. Although a stronger increase of cyanide after oral administration compared to i. v. amygdalin[8] can be expected, it might be necessary to routinely control cyanide in patients subjected to i.v. amygdalin.

The mechanism behind the cyanide increase following amygdalin infusion is not entirely clear. According to the postulated mode of action by amygdalin proponents, cyanide could be released from annihilated tumor cells. However, it cannot be excluded that "pure" amygdalin may be contaminated with traces of β-glucosidase, triggering amygdalin metabolization before it reaches the target cells.

If a cyanide level resulting from oral amygdalin administration is on the threshold to toxicity, i.v. amygdalin administration could push the level over towards toxicity. Still, a toxic cyanide level related to purified amygdalin has not yet been defined. Speijers suggested a value of 5000 μg cyanide/L blood as being lethal.[20] Sauer et al. assumed 200 μg cyanide/L blood as toxic and 3000 μg cyanide/L blood as lethal.[14]. Based on these guidelines, 5 patients in the present evaluation exhibited values > 200 μg cyanide/L after i.v. application. But no patient within this seemingly toxic range exhibited any typical signs of cyanide poisoning.

Since a multivariate analysis of patients experiencing cyanide toxicity identified hyperlactacidemia as the lone significant factor predicting cyanide poisoning,[21] lactate levels were also evaluated in the present study. Unexpectedly, lactate decreased, whilst cyanide increased. Obviously, elevation of cyanide does not induce metabolic acidosis in terms of an increased lactate level. **The reduced lactate level might be explained by an elevation of the lactate degrading enzyme lactate dehydrogenase (LDH). Although no data is available about LDH concentrations in the patients' blood before and after treatment in the present investigation, clinical studies have demonstrated an enhanced serum LDH-level in tumor patients, compared to healthy persons.[22,23] Given an anti-tumor effect of amygdalin, a reduced LDH-level would be expected following amygdalin treatment. However, this mechanism may be masked if amygdalin does indeed destroy tumor cells, leading to an elevated LDH-release due to cell destruction. In this case, the scenario of cyanide poisoning caused by amygdalin would become unlikely.**

The relevance of decreased lactate is not clear. Several reports have documented that lactate positively correlates with tumor progression. Ping et al. demonstrated that lowering lactate may activate T-lymphocyte dependent immune function in gastric cancer.[24] Inhibition of lactate suppressed tumor growth and metastasis in a breast cancer model,[25] and high levels of lactate dehydrogenase have been seen in neuroblastoma patients after relapse and tumor progression.[26] Lowering lactate has been reported to re-sensitize drug resistant tumor cells.[27,28] This is of interest since many patients turn to CAM during chemotherapy or when chemotherapy has failed. A study on lung cancer patients subjected to chemotherapy indicated that a low serum lactate dehydrogenase level was associated with an enhanced probability of survival.[29] Nevertheless, since the present study was not designed to follow-up, we cannot conclude that the decrease in lactate might be due to successful treatment of the cancer. **This is possible though, since several reports were published in the 1960s attesting to "significant" disease arrest or even regression after amygdalin application.[30–32] However, all these investigations have in common that detailed methodological and technical information are not provided. Therefore, these reports present anecdotal, rather than scientifically sound information. Today's assessment of amygdalin's value as a treatment for cancer is based on the Moertel study from 1982, which concluded that amygdalin is ineffective against cancer.[9] Yet, this study too has been criticized, since control groups were not included, follow up was not done, and inactive amygdalin was applied.[33]**

Many questions about the use of amygdalin remain open. This is the first study worldwide comparing the cyanide-lactate-relationship during therapy. It has been carried out on a small patient population and, therefore, cannot be generalized. Studies directed towards determining toxicity due to amygdalin administration and the consequent possibility of cyanide poisoning are urgently required. Studies directed towards determining the validity of lactate levels as an indication of cyanide toxicity during amygdalin application are also urgently required. Since the usefulness of amygdalin has not clearly been proven and a therapeutic regimen has not been established or standardized it is essential that patients not be harmed by either oral or i.v. amygdalin administration. Studies directed towards the efficacy of amygdalin are most urgent, **since it is likely that unknown thousands of patients** receive amygdalin orally and intravenously every year.

Competing interests

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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